PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

NUMBER 28 MAY 2000

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.

Advertisements in independent electronic journals

At the suggestion of the Code of Practice Appeal Board a working party established by the Authority has reviewed the position under the Code of Practice of advertisements in independently produced electronic journals, such as the eBMJ. These advertisements are already covered by the Code, though it does not refer to them specifically. Proposals to amend the Code to clarify the position are being developed.

Guidance prepared by the working party, which has been agreed by the Appeal Board and by the ABPI Board of Management, is set out below to assist companies advertising in independent electronic journals.

1 Advertisements in electronic journals must include the prescribing information as set out in Clause 4.2 of the Code. Abbreviated advertisements are not permitted.

The reason for this is that the content and size of abbreviated advertisements are tightly controlled by the Code which reflects UK law. They are limited in size to 420 square centimetres and can only appear in professional publications sent or delivered wholly or mainly to members of the health professions. It is not possible to assure compliance with the size requirement in an electronic journal. Further, the current supplementary information to Clause 5.2 states that the prescribing information must be made available for any advertisement for a medicine appearing on audio-visual material or in an interactive data system.

2 The first part of an advertisement in an electronic journal, such as the banner, is often the only part of the advertisement that is seen by readers. It must therefore include a clear, prominent statement as to where the prescribing information can be found. This should be in the form of a direct link. The first part is often linked to other parts and in such circumstances the linked parts will be considered as one advertisement.

If the first part mentions the product name then this is the most prominent display of the brand name and the non-proprietary name of the medicine or a list of the active ingredients using approved names where such exist must appear immediately adjacent to the most prominent display of the brand name. The size must be such that the information is easily readable. If the product is one that is required to show an inverted black triangle on its promotional material then the black triangle symbol should also appear adjacent to the product name. The requirement of Clause 10 that promotional material and activities should not be disguised should also be borne in mind.

3 Clause 6.4 limits the numbers of pages bearing advertising for a particular product to no more than three. This was thought to be impractical for advertising in electronic journals. It was decided that if the first part of the advertisement, the banner, or similar, was no larger than 10 per cent of the size of the screen, then links to three further links would be allowed. If the first part of the advertisement was larger than 10 per cent of the size of the screen, then links to two further links would be allowed.

4 The Medicines Control Agency's Advertising and Promotion of Medicines in the UK, Guidance Note No 23, refers to advertising on the Internet. Section 2.2 states that a journal which is published or posted on the Internet and which is expressly stated to be for health professionals is considered to be directed at persons qualified to prescribe or supply medicines and the advertising contained within the journal should comply with Part IV of the Advertising Regulations. Each page of an advertisement for a prescription only medicine should be clearly labelled as intended for health professionals.

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Public reprimand for Schwarz Pharma

Schwarz Pharma has been publicly reprimanded by the ABPI Board of Management as a result of its sponsorship of the publication 'ED Matters'.

Numerous breaches of the Code had been ruled by the Code of Practice Panel which considered that the publication brought discredit upon the industry.

Full details can be found at page 3 in this issue of the Review in the report for Case AUTH/895/7/99.

IFPMA Symposium on the Internet

The International Federation of Pharmaceutical Manufacturers Associations (IFPMA) is to hold the 'Second Global Symposium on Pharmaceuticals and the Internet: Building up New Relationships among Stakeholders' in Geneva on 3 October.

The Symposium will focus on the evolution of the Internet environment, health information over the Internet, prescribing through the Internet, health and safety issues, intellectual property issues and new players.

Details and registration form can be obtained by fax or e-mail to IFPMA.
Fax: 00 4122 338 3299.
E-mail: admin@ifpma.org
Web: http://www.ifpma.org

1999 Levy largely refunded

The Authority is financed principally by a levy payable by members of the ABPI and by administrative charges payable by pharmaceutical companies found in breach of the Code and pharmaceutical companies which make complaints which are not upheld. No charges are payable by complainants from outside the pharmaceutical industry.

In 1999, 75% of the levy due was called up initially in the expectation that this would suffice for the Authority's needs.

In the event, income from administrative charges would have led to an undue surplus on the year and, to avoid that, member companies were refunded 75% of the levy which they had actually paid. The call for the year thus amounting to only 18.75%.

Refunding levy in these circumstances means that the costs of the Authority are borne largely by those pharmaceutical companies which are actually involved in cases.

Following the refund, the Authority had a deficit for the year of £35,431, its income being £442,232 and its expenditure £477,663. Administrative charges came to £343,800, the levy to £60,758 and income from meetings and seminars to £37,674. There were surpluses in 1996, 1997 and 1998.

Enquiry into Internet pharmaceutical crime

The Medicines Control Agency has set up a special enquiry team to conduct a year long study into the nature and extent of pharmaceutical crime committed via the Internet.

All aspects will be investigated and there will be liaison on the matter with enforcement bodies outside the United Kingdom. An ongoing understanding of the levels and types of such crimes will be developed and at the conclusion of the study an assessment will be made to determine the future enforcement activity required.

Advertisements in independent electronic journals

Continued from page 1

The working party did not see the need to include this statement on advertising in an electronic journal such as the eBMJ as it was clearly a journal for health professionals. The paper version, which was available to members of the public, did not include such a statement. The working party decided that this should be discussed with the MCA.

CODE OF PRACTICE TRAINING

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

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

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

Friday, 21 July

Tuesday, 5 September

Thursday, 28 September

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

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

How to contact the Authority

Our address is:

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

Telephone: 020 7930 9677
Facsimile: 020 7930 4554

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

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

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

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

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

CASE AUTH/895/7/99

PFIZER v SCHWARZ PHARMA

Sponsored publication – ED Matters

Pfizer complained about 'ED [Erectile Dysfunction] Matters' which had been sponsored by Schwarz Pharma and published on its behalf. The publication focussed on the proceedings of the XIVth Congress of the European Association of Urology and bore the prescribing information for Schwarz's product, Viridal Duo (alprostadil intracavernosal injection). There were numerous references to Pfizer's product Viagra (sildenafil). Pfizer alleged that ED Matters was a promotional item and made a number of specific allegations. Schwarz contended that it was a service item written by freelance journalists which did not contain a promotional message for Schwarz products. The Panel noted that ED Matters was posted to specialists in erectile dysfunction and also to general practitioners and incontinence advisers who had specifically asked to receive it. Some of the company's representatives carried copies and copies were placed on exhibition stands. The Panel considered that the publication came within the scope of the Code.

A breach of the Code was ruled by the Panel because Pfizer's brand name, Viagra, had been used without its consent. The claim 'Men stick with Injection Therapy' was ruled in breach because the evidence did not support it. The claim that injections '… have no systemic side effects; …' was ruled in breach as systemic effects might occur. It was not sufficient to qualify the claim by means of a footnote. A page headed 'The true impact of Oral Therapy' was considered by the Panel to be misleading and not capable of substantiation and disparaging of Viagra and breaches of the Code were ruled. An article 'Is sex really harmful to a man's health?' which referred to a link between cardiovascular death and the use of Viagra was considered to be misleading and disparaging of Viagra and breaches of the Code were ruled. The claim 'Viagra has a marked 'antihypertensive effect' in men with high blood pressure' was considered by the Panel not to represent the balance of the evidence and was ruled in breach. The Panel considered that the claim 'Viagra is least effective in diabetics and after radical prostatectomy' lowered the reader's expectations of Viagra's efficacy and was disparaging and breaches of the Code were ruled. A breach was also ruled because references to combination therapy were misleading because neither Viridal Duo nor Viagra was licensed for combination therapy.

The Panel noted that it had made a number of specific rulings about the publication. It was concerned that it was misleading with regard to the cardiovascular effects and safety of Viagra. The Panel considered that the publication brought discredit upon and reduced confidence in the pharmaceutical industry and a breach of Clause 2 of the Code was ruled.

As is usual with all cases settled at Panel level, a report was made to the Code of Practice Appeal Board. The Appeal Board was very concerned about the case and decided to report Schwarz to the ABPI Board of Management. The ABPI Board decided to publicly reprimand Schwarz. It also decided that the Authority should carry out an audit of the company's procedures in relation to the Code. Upon receipt of the audit report, the ABPI Board decided that on the basis that Schwarz confirmed that it had taken action on the recommendations in the audit report the matter would be closed. Schwarz provided the necessary confirmation.

Pfizer Limited complained about a six page A4 publication entitled 'ED [erectile dysfunction] Matters' sponsored by Schwarz Pharma Limited.. The publication stated that it was sponsored by Schwarz Pharma and published by a communications agency on behalf of Schwarz. The publication focussed on the proceedings of the XIVth Congress of the European Association of Urology. The publication included a coupon to complete and return to Schwarz in order to receive future issues. Prescribing information for Schwarz's product Viridal Duo was included.

COMPLAINT

Pfizer stated that on examining the publication, despite the disclaimer that 'The views expressed in this publication are not necessarily those of the publishers or Schwarz Pharma', it was clearly a promotional piece sponsored by Schwarz, published by an agency on behalf of Schwarz. The fact that this was a Schwarz promotional piece was underlined by the fact that the back page of the publication consisted of prescribing information for Schwarz's product Viridal (alprostadil intracavernosal injection), which was indicated for the treatment of erectile dysfunction. The publication was therefore within the scope of the Code and fully the responsibility of Schwarz.

1 Use of Pfizer's brand name

Pfizer's brand name Viagra was used at least 21 times throughout the publication, without Pfizer's consent. A breach of Clause 7.10 was alleged. Pfizer stated that this was particularly concerning given the unbalanced and disparaging way in which Viagra was referred to and also served further to underline the promotional nature of the piece.

2 Claim 'Men stick with Injection Therapy'

Pfizer alleged that the main headline claim on page 1 'Men stick with Injection Therapy' was in breach of Clauses 7.2 and 7.3 of the Code as it was not accurate, balanced, fair, objective and unambiguous and was not based on an up-to-date evaluation of all the available evidence. It was not substantiated by the study referred to, in which apparently 'four out of ten men with erectile dysfunction prefer to continue using injection therapy even after trying oral therapy', ie only a minority of men. In any event the claim related to a large collection of patients who were all established on long term injection therapy; not simply patients who had tried one injection and one or two Viagra tablets. The comparison was therefore inappropriate to support the claim and was out of line with even the figure quoted on page 2 that Viagra accounted for 87% of prescriptions for ED.

3 Claim that injections '…have no systemic side effects;*…'

The asterisk referred to a footnote in small print stating that 'on extremely rare occasions, systematic (sic) side effects may occur.' Pfizer stated that this fact could also be seen from the last sentence of the side effects section of the Viridal prescribing information. The claim was therefore a clear breach of Clause 7.7 of the Code and the fact that it was a quotation from a presentation was not sufficient to make it acceptable, as explained in the supplementary information to Clause 11.2. Neither was the use of the small footnote adequate to modify this breach in these circumstances.

4 Page headed 'The true impact of Oral Therapy'

Pfizer stated that whilst the text of page 2 made it clear that Viagra was a widely acceptable therapy – accounting for 87% of prescriptions for ED according to a consultant urologist – the most prominent section, highlighted in a blue box and in larger type, sought to create a very different, misleading and unbalanced impression. The blue box included a quotation referring to patients being 'very worried about the possibility of cardiovascular effects' and having 'a problem with planning sex as [sildenafil] takes one hour to work….'. The denigration of Viagra in this prominent position was unjustified by the balance of the evidence and there was apparently (and to Pfizer's knowledge) no data to support either of these contentions. Cardiovascular effects were discussed further in point 5 below. Viagra did not always take one hour to work. The summary of product characteristics (SPC) stated in section 5.2 that maximum absorption was reached within 30 to 120 minutes although 'approximately one hour' was the recommended dosing (section 4.2).

Also included in the highlighted section was the statement that 'Patients are also reluctant to pay for treatment.' This was clearly intended to suggest that patients would have to pay for Viagra whereas other treatments (ie Schwarz's product) would be provided on the NHS. This of course was not necessarily so; Viagra was, at the time the publication was prepared, legally available on the NHS and, from 1 July 1999, new regulations came into effect restricting the availability on the NHS of all ED treatments without distinction (the National Health Service (General Medical Services) Amendment Regulations 1999, SI No. 1627).

Pfizer alleged that this page breached Clauses 7.2, 7.3 and 8.1 of the Code.

5 Page 3 article 'Is sex really harmful to a man's health?'

The page referred to the much publicised link between cardiovascular deaths and the use of Viagra which generated intense controversy during a Pfizer sponsored satellite symposium. Reference was made to the number of deaths among Viagra users reported to the US Food and Drug Administration (FDA). The page also included a table comparing oral sildenafil (Viagra) with intracavernosal alprostadil and transurethral alprostadil with respect to deaths, number treated and deaths per million treated. The data for sildenafil was from the total number of American and European deaths reported to the FDA up to November 1998.

Pfizer alleged that this article in its entirety contravened Clause 7.2 of the Code. It was a journalistic-type piece describing an impromptu debate at a scientific symposium and in no way could be regarded as accurate, balanced, fair, objective and unambiguous. It was partly because the breaches of the Code in this respect were so numerous that Pfizer believed this article to be unfairly disparaging of Viagra in breach of Clause 8.1 of the Code. The specific problems were as follows:

a The claim in the third paragraph that 'sexual activity has a protective effect on men's health' was entirely inappropriate and misleading in this context. The study cited was a 10 year cohort study which reported that increased orgasmic frequency seemed to have a protective effect on men's health, over a 10 year period. By contrast, the review of safety data concerned renewed sexual activity in men with multiple cardiac risk factors in many cases. Some of these men might not have engaged in sexual activity for a number of years and, following treatment with Viagra, were able to resume it. It was inevitable that such a sudden resumption of sexual activity would present higher risks than sexual activity taking place regularly over a period of ten years. Whilst in the longer term resumed sexual relations might have health and social benefits, in the short term resumption of sexual activity was associated with a small increase in the absolute risk of cardiovascular events. For example, it was recognised that sexual activity increased cardiac workload and that the risk of myocardial infarction increased by a factor of 2.5 in the two hours after sexual activity.

b The exclusion criteria used in Pfizer's clinical trial programme now represented the majority of the contra-indications for Viagra. Therefore, the clinical trial population in Pfizer's studies did actually reflect the real clinical experience since the product's launch. Indeed the data showed that the percentages of concomitant illnesses in the clinical trial population were in fact very similar to the profile in patients treated with Viagra in ordinary clinical practice. It was therefore unfair and misleading to state that the clinical trial exclusion criteria rendered those trial results unrepresentative of Viagra's cardiovascular safety profile in the general population (see e below).

c It was unfair and misleading to use the FDA's post-marketing surveillance data to draw conclusions regarding adverse event rates or safety profiles when comparing different treatments. Many factors could explain differences in reporting rates and these factors would need to be included in the discussion to make the report balanced and unambiguous. These included, for example, the relative amount of publicity, marketing activity and study publication which all commonly increased the rate of adverse event reporting. In a paper by FDA authors analysing the strengths, limitations and applications of the FDA's adverse event reporting system it was stated that:

'One of the greatest limitations of any spontaneous reporting system – and perhaps the one accounting

for the greatest misuse of ADE reporting data – is its inability to provide incidence rates, that is, measures of the proportion of people who are exposed to a drug that will experience a given adverse event. ADE reports do not provide a valid estimate of numerator data. Although the number of reports for a given drug and event can be combined with a measure of drug exposure and expressed as, for example, reports per million prescriptions, such calculations provide us only with estimated reporting rates. Actual incidence rates remain elusive, because of several limitations.'

It also stated:

'Reporting may be stimulated by many factors that are not directly related to the actual occurrence rate of ADEs. Publicity in the mass media or an article in the professional literature often leads to an increase in report volume.'

It was worth noting that Viagra had attracted an unprecedented level of publicity (in both the lay and professional media) compared to other pharmaceutical products. The FDA's own action in putting its safety reports for Viagra on the Internet probably stimulated a unique interest in adverse event reports on the product.

The background to the FDA data and an explanation of its inherent limitations was contained in the relevant sections of the FDA website. The FDA had ceased to update this site since November 1998; however it was still the case that the FDA had not changed its perspective concerning the safety of Viagra.

d Pfizer understood that the '400 deaths' figure (the total number of deaths associated with Viagra) came from third party requests to the FDA for information under the US Freedom of Information legislation rather than any published data. When information was obtained in this way from the FDA, it was sent with a covering letter including the following:

'For any given report, there is no certainty that the suspected drug caused the reaction. This is because physicians are encouraged to report suspected reactions. The event may have been related to the underlying disease for which the drug was given to concurrent drug being taken or may have occurred by chance at the same time the suspected drug was taken.'

'Accumulated case reports cannot be used to calculate incidence or estimates of drug risk.'

'Numbers from these data must be carefully interpreted as reporting rates and not occurrence rates. True incidence rates cannot be determined from this database. Comparisons of drugs cannot be made from these data.'

It was clear that in ED Matters, this type of spontaneous report data on Viagra had been used to draw comparisons with other medicines and conclusions about adverse event incidence rates. Pfizer drew attention to the data in the table comparing deaths and the number treated which it alleged was invalid and misleading.

e The boxed text, highlighted on page three, concerning the opinion of the American College of Cardiology (ACC) and the American Heart Association (AHA), was particularly misleading and unbalanced. Firstly, there was an apparent typing error which, even if unintended, created a very misleading impression, stating simply that 'The document states that the use of Viagra is absolutely contraindicated.' The impression was created that Viagra was absolutely contraindicated in cardiac patients generally, which of course was not the case. The sentence had apparently been wrongly divided and presumably intended to state that the use of Viagra was absolutely 'contraindicated in patients taking any chronic nitrate drug therapy', which would be correct. Furthermore, the highlighted text listed five groups of patients in whom the use of Viagra was 'potentially hazardous'. These being patients with active coronary ischaemia, patients with congestive heart failure, patients with low blood volume and low blood pressure status, patients on multiple antihypertensive treatments and patients taking medicines which prolonged the half life of Viagra. Pfizer stated that none of these were consistent with the product labelling for Viagra in either the USA or the European Union. In this regard reference was made to sections 4.3 (contraindications) and 4.4 (special warnings and precautions for use) of the Viagra SPC, it could be seen that Viagra was contraindicated in patients with severe cardiovascular disorders such as unstable angina or severe cardiac failure and in patients with hypotension (blood pressure below 90/50mmHg). The SPC also stated that 'prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity.' This general warning statement clearly applied to all forms of treatment for ED and this had not been reflected in this plainly unbalanced piece focusing only on Viagra. It was also interesting to note that in an interview with the co-chair of the ACC/AHA panel which developed the statement, the same categories of patients referred to in the publication were listed. It then had the following statement: 'In any of these categories, we encourage the physician to make an individual assessment …. It is, however, possible to start any of these patients on a low dose [25mg] of sildenafil and then evaluate tolerance … If these patients don't experience any serious adverse effects, the dose may be increased to 50mg.' This, in Pfizer's view, underlined the misleading nature of the way the information was presented in ED Matters.

f The clear intention behind this page was to disparage Viagra's cardiovascular safety profile and raise concerns in that regard, particularly in comparison with other ED treatments such as Schwarz's own product. As explained above, the reasoning used in the piece was flawed and misleading. Furthermore, the contention did not clearly reflect all the available evidence. For example, a review of the overall cardiovascular profile of Viagra concluded that during clinical trials the incidence of serious cardiovascular adverse events, including stroke and myocardial infarction, was the same for patients treated with Viagra or placebo. Since the product's launch, the number and pattern of spontaneous reports of cardiovascular-related events had been broadly similar

to those observed during clinical development. Similar findings were reported at the 1999 meeting of the American Urological Association.

6 Claim 'Viagra has a 'marked antihypertensive effect' in men with high blood pressure'

The claim, on page 4, which appeared as a heading in a blue box referred to a report of a single, open study of Viagra in a 'small number' of men (the actual number was not stated and the study had not been published as yet). This report was misleading, unfair and unbalanced and did not reflect all the evidence. Pfizer alleged that the study was inconsistent with Pfizer's blinded, comparative, placebo-controlled studies where blood pressure changes observed were small and did not produce adverse events. This piece was therefore also clearly in breach of Clause 7.2 of the Code.

7 Page 5

a One section of the page was headed 'Viagra is least effective in diabetics and after radical prostatectomy'. Pfizer alleged that the claim was again misleading and unbalanced in the way it was presented. Whilst the figures quoted were broadly accurate, the manner in which the headline was used was clearly intended to lower the reader's expectations of Viagra's efficacy generally. The product was in fact effective in ED across all aetiologies, to varying degrees, as was clear from the SPC. Pfizer alleged breaches of Clauses 7.2 and 8.1 of the Code.

b In relation to a box headed 'Combining therapies for even greater benefit', it should be noted that there were no such combination therapies currently licensed for the treatment of ED. According to section 4.4 of the Viagra SPC, the use of combinations of Viagra and other treatments for ED 'is not recommended'. There was also a reference in the prescribing information for Viridal (under 'Interactions') to the fact that certain other medicines inducing erections should not be used in parallel with Viridal Duo. Pfizer alleged that this section of ED Matters was potentially misleading in breach of Clauses 7.2 and 3.2 of the Code.

8 ED Matters in its entirety

Pfizer alleged that the publication as a whole breached Clauses 7.2 and 8.1 due to its lack of balance and entirely negative, disparaging focus on Viagra. This focus and the impression of Viagra consequently conveyed was entirely inconsistent with the evidence available which demonstrated clearly that Viagra was an effective treatment for ED which was well tolerated and highly acceptable to patients.

Not surprisingly, Pfizer was extremely concerned about ED Matters. Given the seriousness and large number of the breaches of the Code and the fact that it had already been distributed, presumably as a one-off, to healthcare professionals, it had not sought to contact Schwarz prior to submitting the complaint. For these reasons, it also believed that Clause 2 of the Code had been breached in that it discredited the pharmaceutical industry as a whole.

RESPONSE

Schwarz stated that ED Matters was a publication designed to be a fast reporting service of current topics of interest and debates in the field of erectile dysfunction. The publication was sponsored by Schwarz and was marked as such, as it would be misleading not to admit sponsorship. The issue of ED Matters in question reported the proceedings of the XIVth Congress of the European Association of Urology. As the function of the publication was one of reporting and informing rather than promotion, the company did not accept that it could be described as promotional material. The focus of the issue on Viagra reflected accurately the current issues and concerns relating to those involved in the treatment of ED and which the Congress discussed. As these were reported accurately, it negated the concern of Pfizer that Viagra was referred to frequently. It was made clear on the front page that the views were not those of Schwarz but the opinions and views of the medical professionals at this meeting. At no point was there any promotion of Viridal Duo. Indeed, in the blue box at the top of page 2, oral therapy was clearly referred to as first-line treatment and further down the page intracavernous treatment (such as Viridal Duo) was described as second-line. The fact that the publication was reporting debate was clearly demonstrated in the article on page 3, which presented both sides of the current controversy surrounding the safety of restarting sexual activity. ED Matters was, therefore, clearly not a promotional item, but was designed as a newsletter highlighting the issues and debate surrounding the treatment of ED.

As ED Matters was simply a reporting organ to inform interested professionals of current topics in the field of erectile dysfunction and not a promotional item, Schwarz submitted that the various points raised by Pfizer were neither appropriate nor valid. For this reason, it chose not to respond to the individual concerns.

CONSIDERATION BY PANEL

The Panel noted that Schwarz had not responded to the allegations in full and should be asked to do so.

FURTHER RESPONSE FROM SCHWARZ PHARMA

Schwarz stated that ED Matters was written by freelance journalists and edited and published by an agency at the behest of Schwarz as a service item to those involved in the treatment of erectile dysfunction. Schwarz's involvement in this process was merely one of internal approval to ensure the accuracy of the reporting. As far as the relationship between Schwarz and the publisher was concerned, the agency was also involved in a range of other activities at the request of Schwarz.

ED Matters was primarily distributed as a service item by mailings to ED specialists. The current mailing list had 1030 recipients in total. Additionally, ED Matters was sent to GPs and incontinence advisors who had specifically requested to receive it. There were currently 1,276 GPs and 79 incontinence advisors on this mailing list. The recipients were able

to request to be added to the mailing lists for ED Matters when it went out as an insert in 'Trends' magazine.

Schwarz's ED Healthcare representatives did have copies available as a service item, but as their customers had already received them, it tended to be extra copies that were provided by the representative. Similarly ED Matters was put on exhibition stands from time to time alongside other publications such as abstracts and items such as sharp boxes, needle clippers, patient and educational videos (like the RCN ED Video) as part of its general service to ED Healthcare. It was important to note that the company's normal GP field force did not receive ED Matters to distribute. Non-specialists must specially request the publication.

Finally the company stressed again that ED Matters did not purport to be an academic publication, but reported accurately, on actual debate around current 'hot topics' in the field of erectile dysfunction as it occurred in congresses for example. It did not contain a promotional message for Schwarz products.

FURTHER CONSIDERATION BY PANEL

The Panel noted that ED Matters was written by freelance journalists and edited and published at the request of Schwarz. It was distributed as a service item by mailing to specialists in erectile dysfunction and to GPs and incontinence advisers who had specifically requested to receive it. Some of the company's representatives carried copies and copies were placed on exhibition stands.

The Panel considered that the publication came within the scope of the Code. It had been used for a promotional purpose. Schwarz would need to respond to the allegations so that the complaint could be considered.

FURTHER RESPONSE FROM SCHWARZ PHARMA

As stated before, ED Matters was always intended to be a service item. It was written and edited by independent parties with a view to education, information and reporting on current issues and thus, in the company's opinion, outside the scope of the Code. As it was considered to be non-promotional it was never produced with the limitations of the Code in mind. Schwarz did not consider that it would be appropriate to attempt to defend the item within the remit of the Code. The company stated that, being that the Panel had decided that ED Matters was within the scope of the Code, the decisions should be made on Pfizer's complaint rather than any after the fact arguments on Schwarz's part. However, in light of the above, and if it was accepted the ED Matters was indeed promotional, the company believed that the matter should be addressed as one single potential breach of 7.2 rather than individual breaches.

Schwarz had now withdrawn its support from any future editions of ED Matters.

PANEL RULING

The Panel noted that it had already decided that ED Matters came within the scope of the Code. The publication was produced at the request of Schwarz and had been distributed by the company. It was possible for a company to sponsor material which mentioned its own products and not be liable under the Code for the content but only if it had been a strictly arm's length arrangement with no input by the company and no use by the company of the material for promotional purposes. The Panel considered that Schwarz was responsible for the content of ED Matters. It had been produced at the request of Schwarz and had been distributed by the company which maintained the mailing list. The publication had to comply with all the requirements of the Code.

The Panel noted Schwarz's request that the complaint should be addressed as one single breach of the Code. It had, however, to consider the allegations as made and could not agree to Schwarz's request.

1 Use of Pfizer's brand name

The Panel ruled a breach of Clause 7.10 as Pfizer's brand name, Viagra, had been used without prior consent.

2 Claim 'Men stick with Injection Therapy'

The Panel ruled breaches of Clauses 7.2 and 7.3 as alleged.

3 Claim that injections '...have no systemic side effects,...'

The Panel considered that this claim was misleading as systemic effects might occur. It was not acceptable to qualify the claim by the use of a footnote. A breach of Clause 7.7 of the Code was ruled.

4 Page headed 'The true impact of Oral Therapy'

The Panel considered that this page was misleading and not capable of substantiation. Breaches of Clauses 7.2 and 7.3 were ruled. The Panel also considered that the page disparaged Viagra and a breach of Clause 8.1 of the Code was ruled.

5 Page 3 article 'Is sex really harmful to a man's health?'

The Panel noted the points raised by Pfizer and considered that the page was misleading. A breach of Clause 7.2 of the Code was ruled. The page also disparaged Viagra and a breach of Clause 8.1 of the Code was ruled.

6 Claim 'Viagra has a 'marked antihypertensive effect' in men with high blood pressure'

The Panel noted that this open study had been carried out in a small number of men with high blood pressure. It had not been provided with any information about the study by Schwarz. The Panel noted that Section 4.1 of the SPC for Viagra stated that sildenafil had vasodilator properties resulting in mild

and transient decreases in blood pressure. The SPC indicated that in clinical trials sildenafil had been administered to patients with hypertension. The Panel decided that the section did not represent the balance of the evidence and a breach of Clause 7.2 of the Code was ruled.

7 Page 5

The Panel noted that Viagra was effective in ED across all aetiologies to varying degrees. It considered that the claim 'Viagra is least effective in diabetics and after radical prostectomy' lowered the reader's expectations of Viagra's efficacy and was disparaging. Breaches of Clauses 7.2 and 8.1 of the Code were ruled.

The references to combination therapy were misleading given that neither Viridal Duo nor Viagra was licensed for combination therapy. A breach of Clause 7.2 of the Code was ruled.

8 ED Matters in its entirety

The Panel noted that it had made a number of specific rulings about the publication. It was concerned that the publication was misleading with regard to the cardiovascular effects and safety of Viagra. The Panel considered that the publication brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 of the Code was ruled.

APPEAL BOARD

As is usual with all cases settled at the Panel level, a report was made to the Code of Practice Appeal Board in accordance with Paragraph 4.1 of the Constitution and Procedure.

The Appeal Board was very concerned about this case and decided that it would report Schwarz to the ABPI Board of Management. This was in accordance with Paragraph 11.1 of the Constitution and Procedure.

REPORT TO THE ABPI BOARD OF MANAGEMENT

The ABPI Board was concerned not only that the company had not considered that ED Matters was promotional but also that misleading statements had been made in relation to safety issues. The Board decided that Schwarz should be publicly reprimanded. The ABPI Board instructed the Authority to carry out an audit of the company's procedures in relation to the Code. This was in accordance with Paragraph 11.2 of the Constitution and Procedure.

Upon receipt of the audit report, the ABPI Board considered that on the basis that Schwarz confirmed that it had taken action on the recommendations in the audit report, the matter would be closed. Schwarz provided the necessary confirmation.

Complaint received	**6 July 1999**
Case completed	**21 September 1999**
PMCPA proceedings completed	**14 October 1999**
ABPI Board proceeding completed	**25 February 2000**

TRUSTEES OF THE NATIONAL ASTHMA & RESPIRATORY TRAINING CENTRE v BOEHRINGER INGELHEIM

Sponsorship of the Respiratory Education Resource Centres

The Trustees of the National Asthma & Respiratory Training Centre (NARTC) submitted a complaint about the activities of Boehringer Ingelheim which had been involved with the establishment of the Respiratory Education Resource Centres (Respiratory ERC).

The NARTC was a charity started in order to train health professionals in the management of asthma. The courses covered a range of respiratory disease including chronic obstructive pulmonary disease (COPD).

The NARTC was concerned about the activities of Boehringer Ingelheim in relation to the Respiratory ERC. A number of concerns were raised about the arrangements, materials and role of Boehringer Ingelheim. All of the allegations were denied by Boehringer Ingelheim which provided detailed information, as did the Respiratory ERC. The final outcome was that there had been no breach of the Code.

The Panel ruled a breach of the Code as, in its view, the involvement of Boehringer Ingelheim with a course manual had not been made clear. Upon appeal by Boehringer Ingelheim further information was provided about the manual which was a substantially redrafted version of the original version commissioned by Boehringer Ingelheim. The Appeal Board considered that in the circumstances the involvement of Boehringer Ingelheim had been made sufficiently clear and no breach of the Code was ruled.

The Panel also ruled a breach of the Code as it considered that given the extent of Boehringer Ingelheim's involvement, readers of various materials and those considering enrolling in the courses should have been aware of it. The Panel noted that it was not necessarily unacceptable for Boehringer Ingelheim to be involved and there was no evidence that anything improper had occurred. Upon appeal by Boehringer Ingelheim the Appeal Board considered that the relationship between the Respiratory ERC and Boehringer Ingelheim was not such that it needed to be declared in any more detail than had been done. No breach of the Code was ruled.

The Panel considered that the Respiratory ERC training programme would enhance patient care and benefit the NHS. The training programme was not linked with the use of any medicine in particular. The Panel ruled no breach of the Code in that regard.

The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was reserved as a sign of particular censure and this was appealed by the NARTC. The Appeal Board noted its rulings of no breach of the Code and did not consider that there had been a breach of Clause 2.

The Trustees of the National Asthma & Respiratory Training Centre (NARTC) submitted a complaint about the activities of Boehringer Ingelheim Limited.

The NARTC explained that it was a charity started in 1986 in order to train health professionals in the management of asthma. More than 20,000 health professionals had been trained. The courses now covered a range of respiratory disease including the chronic obstructive pulmonary disease (COPD) course which was implemented in 1996. The training centre had received a number of awards for its work and had gained educational grants for a range of projects from every pharmaceutical company with a respiratory portfolio, often obtaining multi-company sponsorship. The NARTC had always had an extremely good working relationship with the companies, which had behaved in a supportive and professional manner.

COMPLAINT

The complainants stated that over the last 18 months the NARTC had been concerned about the activities of Boehringer Ingelheim. In 1997 the NARTC Director was told by Boehringer Ingelheim that the company was intending to invest £2 million in setting up four respiratory training centres across the UK. Boehringer Ingelheim had developed its own chronic obstructive disease training programme, though it was fully aware of the NARTC COPD course. The company had previously donated sponsorship to help professionals to undertake the NARTC COPD course and the NARTC had trained Boehringer Ingelheim personnel in COPD.

The NARTC stated that it corresponded and had several meetings with Boehringer Ingelheim with the aim of ensuring that training remained in the hands of independent charities such as the NARTC. The meetings were not successful, and Boehringer Ingelheim admitted to having 'commercial and not entirely altruistic reasons' for embarking on this project. No minutes were taken at this meeting, but the complainants referred to a letter to Boehringer Ingelheim from the NARTC. No acknowledgement or response was received.

The complainants stated that since that time Boehringer Ingelheim had approached various opinion leaders with its course and offers of substantial funding and had cut funding to the NARTC. Boehringer Ingelheim had now successfully recruited a hospital which would be the centre housing its project. The consultants recruited were members of the working group which drew up the British Thoracic Society (BTS) National Guidelines for COPD, a condition in which Boehringer Ingelheim had a large product interest.

The complainants stated that Boehringer Ingelheim had set up a company called the Respiratory

Education Resource Centres (Respiratory ERC) at the hospital which had received charitable status.

The complainants had the following major concerns:

- The Respiratory ERC training materials had been produced by a medical education agency appointed by Boehringer Ingelheim and bore the Boehringer Ingelheim copyright.
- Brand names for products had specifically been avoided in the literature in accordance with the Code. However, the NARTC's view was that healthcare professionals needed to be informed about both brand and generic names as part of their education. As an independent organisation the NARTC was at liberty to do this. It appeared to the NARTC that the Respiratory ERC did not therefore regard itself as an independent organisation.
- The NARTC had been informed that two Boehringer Ingelheim staff were on secondment from Boehringer Ingelheim but still employed by the company.
- Companies House listed two of the six Trustees of the Respiratory ERC as Boehringer Ingelheim employees.
- The NARTC stated that in addition to the large sum of money donated to the hospital to set up the Respiratory ERC concept on behalf of Boehringer Ingelheim, it was part-sponsoring health professionals to attend Boehringer Ingelheim's copyrighted course.
- The NARTC was concerned that Boehringer Ingelheim proposed to withdraw financial support from a medical journal if a member of the NARTC staff was used to judge a Boehringer Ingelheim sponsored competition. The information came from the editor of the journal who did not wish to be identified.
- The Respiratory ERC had placed a huge number of advertisements in the medical press; the NARTC had been told that this was done by Boehringer Ingelheim's advertising/public relations agency. The advertisements did not state Boehringer Ingelheim's involvement, though the press release did.

The NARTC had been told that the Respiratory ERC launch PR campaign had been driven by Boehringer Ingelheim's public relations agency. The information projected via this publicity was misleading. The Healthcare Parliamentary Monitor, commenting on the setting up of the Respiratory ERC, implied that the courses were unique, when in fact the NARTC had been training health professionals in both asthma and COPD for a number of years.

The complainants alleged that it was the spirit of the Code that had been broken by Boehringer Ingelheim. It had placed expert health professionals in the field of asthma and COPD, who previously worked closely together, in an uncomfortable, confrontational position.

The complainants alleged that the Respiratory ERC could not possibly be an independent charity when it was largely funded, driven, staffed and overseen by Boehringer Ingelheim personnel. The complainants stated that if this type of activity was seen as acceptable within the pharmaceutical industry, it would set a worrying precedent for in-depth academic training for healthcare professionals in the future, in all disease areas.

RESPONSE

Boehringer Ingelheim denied any breach of the Code and pointed out that for the most part the statements made by the complainants were inaccurate and misleading. Although it recognised that several of the statements were, in a strict sense, factually correct, they did not constitute a breach of the Code. However, even these did not reflect a balanced observation of the whole picture.

Boehringer Ingelheim had enjoyed a positive working relationship with the NARTC along with many other educational organisations for a number of years. During 1998 and 1999 Boehringer Ingelheim offered support to the NARTC to sponsor 180 course places for practice nurses at a total cost of £35,600 and continued to do so. It was saddened that the NARTC Trustees considered it necessary to take this action, but it welcomed the opportunity to address the issues raised. Hopefully, in doing so, it would allay the complainants' concerns.

It would appear from the complaint that the Trustees of the NARTC had been seriously misinformed regarding a number of issues. Their letter made the following allegations:

1 Boehringer Ingelheim admitted to having 'commercial and not entirely altruistic reasons…'

Boehringer Ingelheim had asked the individuals involved in the meetings with the NARTC as to whether the above was ever stated. No one asked had any recollection of this statement, nor could any meeting minutes be found. However, Boehringer Ingelheim emphasised that it was considering the project because it believed from market research that healthcare professionals wanted additional training in respiratory medicine (in particular COPD) and that they displayed different preferences toward the methods employed in delivery of education generally.

2 Boehringer Ingelheim had set up the Respiratory ERC and had applied for and received charitable status for it

Boehringer Ingelheim denied this allegation. It understood that the Respiratory ERC paid all fees relating to the incorporation of the company and employed local lawyers to review the legal proceedings of the company incorporation and charitable trust application.

3 Boehringer Ingelheim had approached various opinion leaders with its course and offers of substantial funding

Boehringer Ingelheim strenuously denied the allegation that it had approached opinion leaders with its course and offers of substantial funding. Boehringer Ingelheim did not own or run the course

and was somewhat bemused by the reference to the course in the letter of complaint.

It could only assume that this confusion might have arisen as two Boehringer Ingelheim employees were currently on secondment at the Respiratory ERC. Inevitably, in the course of their work at the Respiratory ERC, they had contact with opinion leaders regarding the courses the Respiratory ERC offered through its Diploma of Higher Education in Respiratory Disease Management.

4 Boehringer Ingelheim recruited the hospital and suggested that two of the consultants were 'targeted' because of their involvement in the BTS National Guidelines for COPD

Boehringer Ingelheim denied this allegation. In the autumn of 1997 Boehringer Ingelheim was considering a project proposal to develop three respiratory training centres in the UK (it was at this point that Boehringer Ingelheim visited the NARTC to discuss the Boehringer Ingelheim proposal). Proposed sites were Reading, Manchester and Scotland. The idea was to offer a different type of course to that offered by the NARTC, which would cover more fully the practical aspects of COPD, and would complement rather than replace or compete with the NARTC course.

At the same time the consultants based at the hospital in question were having similar thoughts. The clinical director contacted Boehringer Ingelheim and asked to meet to discuss establishing a national respiratory educational programme. A fellow consultant was also present at this meeting.

During the various discussions which took place it was decided that, to ensure independence from all parties concerned, a new independent organisation should be established. Two doctors were nominated by their medical colleagues to take on the role of project leaders and to become directors of the new organisation once it was established.

5 Boehringer Ingelheim owned the copyright for the Respiratory ERC's COPD manual

This statement was true. The COPD manual was commissioned by Boehringer Ingelheim from a medical educational agency prior to the Respiratory ERC being established. A scientific advisory board, consisting of both medical and nursing personnel appointed by the clinical directorate of the Respiratory ERC, reviewed the COPD manual to ensure its content was accurate and unbiased before it was printed. This course manual had also been accredited independently by a university further reflecting the independent nature of the manual and its academic standing.

It was agreed that as Boehringer Ingelheim had commissioned the manual it should retain the copyright of the document until such time that it required modification. Once modified, the copyright for the COPD manual would pass to the Respiratory ERC. The Respiratory ERC had been granted an exclusive licence to use the material.

Boehringer Ingelheim had never attempted to disguise the fact that it retained the copyright which was clearly stated on the first page of every course manual produced. The placing of a copyright notice on such a document was good practice and indeed was a pre-requisite for preserving and enforcing intellectual property rights.

During a Respiratory ERC presentation to the pharmaceutical industry in September 1998, this issue was raised and the reasons for copyright status explained. The Respiratory ERC offered the manual to all the pharmaceutical companies for comment at this time.

Boehringer Ingelheim had been asked by the Authority to submit copies of the Respiratory ERC's training materials. However, whilst it was the legal owner of the copyright for the COPD manual it did not own the materials and, in any event, had granted an exclusive licence for use of the materials to the Respiratory ERC. Any requests regarding their materials had to be made directly to the Respiratory ERC.

6 Brand names had been specifically avoided in the literature

Boehringer Ingelheim believed that this was a recommendation of the scientific advisory board, which reviewed the course material prior to publication. This was consistent with the BTS Guidelines for the Management of COPD which also did not refer to brand names.

The complainants stated in their letter that the exclusion of brand names suggested that the Respiratory ERC did not view itself as an independent organisation. Boehringer Ingelheim was unable to offer an opinion on how the Respiratory ERC perceived itself and had referred this to the Respiratory ERC for comment.

7 Secondment of two staff members to the Respiratory ERC

This statement was true. Boehringer Ingelheim had seconded two staff members on a fixed term secondment which was due to be reviewed in 1999.

It was not unusual for industry to second employees to an external organisation. One of the Boehringer Ingelheim staff had been responsible for the project planning and Boehringer Ingelheim understood that the collective view of the Trustees was that their experience and expertise would be of great benefit to the charity during its first year of trading.

The two staff had clear roles and responsibilities whilst working for the Respiratory ERC, as defined by the Trustees of the organisation and the contracts of secondment. They were accountable on a day to day basis to the Chairman of the Trustees.

8 Two of the six Trustees of the Respiratory ERC were Boehringer Ingelheim employees

This was true. However, Boehringer Ingelheim denied that this constituted any wrongdoing on its part. It also resented any inference of undue influence on its part. Again the statement did not represent the complete picture. For example, the letter failed to

mention that two of the Trustees were employed by the Chest Centre, the other party involved in setting up the project. The remaining two Trustees had no allegiance to either Boehringer Ingelheim or the Chest Centre. They were a university professor and a lecturer.

As the Trustees of the NARTC would be aware, the role of the charity trustee carried its own responsibilities and trustees had a legal and moral obligation to work in the best interests of the charity at all times. It understood, from the two Trustees who were Boehringer Ingelheim employees, that these Trustees had been given guidance from the Respiratory ERC regarding their independent positions and Boehringer Ingelheim confirmed that it had not attempted and would never attempt to influence them in their capacity as Respiratory ERC Trustees.

Furthermore, the Charities Commission was fully aware of the funding provided by Boehringer Ingelheim to the Respiratory ERC to cover its set up and running costs and had approved the composition of the Board of Trustees.

9 Boehringer Ingelheim had donated a large sum of money to the hospital to set up the Respiratory ERC on its behalf

Boehringer Ingelheim wished to make it clear that it had never donated money to the hospital for this purpose.

10 Boehringer Ingelheim was intending to invest a large sum of money in the project

The sum of money donated to the Respiratory ERC was confidential but was substantially less than the figure in the letter of complaint.

The accounts of the Respiratory ERC remained the property of the Respiratory ERC. However, at the end of its first year of trading Boehringer Ingelheim presumed that the accounts would have to be submitted to Companies House and would then be open to public scrutiny. It presumed that it would be clear from these accounts that Boehringer Ingelheim's grant was, as it had stated above, substantially less than the sum referred to.

11 Boehringer Ingelheim was part-sponsoring health professionals to attend the Respiratory ERC's COPD module for which it owned the copyright

This statement was biased in that it failed to mention that Boehringer Ingelheim had provided and continued to provide part-sponsorship for COPD courses run by the NARTC, AMC Training in Liverpool and the Asthma Education Unit at Kings Mill Hospital. As mentioned above, Boehringer Ingelheim supported 180 places on the NARTC course alone for a total of £35,600 during 1998 and 1999.

12 Boehringer Ingelheim proposed to withdraw financial support from a medical journal if a member of the NARTC staff was used to judge a Boehringer Ingelheim sponsored competition

Without further details, Boehringer Ingelheim could not answer this allegation. However, from its enquiries, it was not aware of any such threat having been made. Boehringer Ingelheim would never condone such a threat.

13 Boehringer Ingelheim's advertising/PR agency had placed a number of advertisements in the medical press. The advertisements did not state Boehringer Ingelheim's involvement but the press release did

This allegation was misleading. It understood that the Respiratory ERC used the same media buyer as Boehringer Ingelheim, but Boehringer Ingelheim had not had any involvement in the placement of advertisements in the medical or nursing press for the Respiratory ERC. It did not believe the Respiratory ERC used the same PR agency as Boehringer Ingelheim.

Since the Respiratory ERC was responsible for advertisements and press releases, this was something which the Respiratory ERC should respond to.

14 The Respiratory ERC's launch campaign was driven by Boehringer Ingelheim

This statement was misleading. The Respiratory ERC approached Boehringer Ingelheim in December 1998 for ideas regarding PR as it had had little response to its own efforts to generate PR locally for the launch event in January 1999. Boehringer Ingelheim referred the Respiratory ERC to a named PR agency whom it understood dealt with the launch PR campaign on behalf of the Respiratory ERC.

Boehringer Ingelheim had contacted the Respiratory ERC regarding the letter of complaint, as some of the allegations made related directly to its organisation. In a letter of response, the Respiratory ERC stated clearly that as an independent educational organisation any requests concerning Respiratory ERC properties or information regarding its working practices should be made directly to it. The Respiratory ERC also extended an invitation to the Authority to contact it directly for any further information.

Boehringer Ingelheim also understood that the Trustees of the Respiratory ERC would be responding directly to the NARTC.

For the purpose of completeness, to the extent not already addressed above, Boehringer Ingelheim dealt with the specific clauses of the Code.

Clause 2

Boehringer Ingelheim stated that the subject matter of this complaint did not concern activities or materials associated with promotion, rather they were purely educational. If, which was denied, they were held to concern promotion, it also denied that they were such as to bring discredit upon, or reduce confidence in, the pharmaceutical industry.

Firstly, to the extent that expert health professionals in the field of asthma and COPD had been placed in the 'uncomfortable confrontational position', it believed

this had been brought about by the NARTC rather than as a result of any activities by Boehringer Ingelheim or the Respiratory ERC.

Secondly Boehringer Ingelheim rejected any suggestion that the Respiratory ERC was not an independent charity and was 'largely funded, driven, staffed and overseen by Boehringer Ingelheim personnel'. The Respiratory ERC was a charitable trust and as such was governed by legislation covering the conduct of trustees. The Board of Trustees 'drove' the Respiratory ERC as well as 'overseeing' its activities as an independent charity. It seemed to Boehringer Ingelheim that the composition of the Board would ensure that there was no conflict of interest with any single party. The staffing of the Respiratory ERC was not governed by Boehringer Ingelheim (seconded employees of Boehringer Ingelheim reported to the Chairman of the Trustees).

Clause 9.1

Boehringer Ingelheim believed that the activities and materials were of a high standard. Nothing in the materials seen by Boehringer Ingelheim should cause offence. It would hope that the Panel would be satisfied in this regard by reviewing, in particular, the advertisements which had appeared in Practice Nurse and Practice Nursing. As far as it was aware, none of the advertisements referred in any way to Boehringer Ingelheim and simply advertised modular courses in respiratory care for health professionals. It was difficult to see what could possibly be offensive in such advertisements. Further, as mentioned above, the course offered by the Respiratory ERC was a university accredited course and had been approved by the Respiratory ERC Scientific Advisory Board.

Clause 9.9

The educational materials related to COPD generally and did not refer to medicines and their uses. If, which was denied, such material did relate to medicines and their uses and was, which was also denied, sponsored by Boehringer Ingelheim, then it believed that to the extent required, Boehringer Ingelheim had clearly indicated that it had 'sponsored' such material. In this regard, Boehringer Ingelheim referred to the Respiratory ERC Diploma programme, (a copy of which was provided) which acknowledged the fact that the Respiratory ERC was 'grateful for the help of a generous grant from Boehringer Ingelheim to set up the organisation and to many other pharmaceutical companies that have offered their support since'. In addition, as mentioned above, the first page of every COPD course manual used on the course contained a notice acknowledging that copyright was owned by Boehringer Ingelheim.

Clause 18.1

Boehringer Ingelheim vigorously denied that its relationship with the Respiratory ERC constituted a gift, benefit in kind or pecuniary advantage which had been offered or given to members of the health professions or to administrative staff as an inducement to prescribe, supply, administer or buy any medicine. The Respiratory ERC was a reputable charity and Boehringer Ingelheim denied that any level of support referred to above would constitute an unacceptable activity under this clause or, indeed, under any other clause of the Code.

Boehringer Ingelheim provided additional information about the two members of staff seconded to the Respiratory ERC since 1 November 1998. It was expected that the two people would resume full time employment with Boehringer Ingelheim at some point in the future. The initial term of the secondment was to finish in October 1999 but might be extended through the first quarter 2000. During the secondment the salaries were paid directly by Boehringer Ingelheim. The seconded staff both worked four days per week directly on the Respiratory ERC business and one day per week for Boehringer Ingelheim. The Chairman of the Trustees was responsible for establishing work objectives and performance appraisals.

INFORMATION RECEIVED FROM THE RESPIRATORY ERC

A detailed letter was received from the Respiratory ERC which at that time stated that its comments remained private and confidential and that the documentation supplied should not be passed to the complainants or any other third party.

PANEL RULING

The Panel considered that this was a difficult case. There was a difficulty with the confidentiality of the comments from the Respiratory ERC.

The Panel noted that Boehringer Ingelheim had played an important role in the establishment of the Respiratory ERC which hoped to be self financing in a couple of years. Details of the start up costs had not been given. Financial information would be made public in due course. The Respiratory ERC had stated that financial assistance had been received from a number of pharmaceutical companies. The Panel noted the large amount of support given to the Respiratory ERC by Boehringer Ingelheim and queried whether the organisation would be seen to be entirely independent of the company given that two of Boehringer Ingelheim's directors were Trustees and that two of Boehringer Ingelheim's staff were at present seconded to the Respiratory ERC. In the Panel's view, there was a difference between sponsoring an organisation by giving it a grant and having no further input, and providing a grant, ongoing support, training materials and staff, as in this case.

The Panel then dealt with each of the issues raised by the NARTC.

The Panel did not consider that it was necessarily unacceptable for Boehringer Ingelheim to have provided the Respiratory ERC training materials and for the materials to bear the Boehringer Ingelheim copyright. Clearly the content had to be appropriate but there was no complaint about that. The COPD manual had been reviewed by a scientific advisory board appointed by the Respiratory ERC. The course

manual had also been accredited independently by a university. The manual had been offered to all pharmaceutical companies.

The Panel did not accept that the fact that brand names had not been included in the literature meant that the Respiratory ERC did not regard itself as an independent organisation. There were a number of factors that had to be taken into account when deciding whether something was promotional or not. In the Panel's view it was the content, including, for example, what was said about products, that was a relevant factor, not that using brand names meant that the material was promotional. It was possible to promote a product by generic name and in some instances to promote a medicine without actually naming it at all.

The Panel noted that two of the six Respiratory ERC Trustees were also Boehringer Ingelheim directors. In addition two employees had been seconded to the Respiratory ERC, working four days a week for the Centre and one day a week for Boehringer Ingelheim; the whole of their salaries was paid by Boehringer Ingelheim.

In the Panel's view it was not necessarily unacceptable for Boehringer Ingelheim to sponsor health professionals to attend the course.

The Panel was very concerned about the allegation that Boehringer Ingelheim had proposed to withdraw financial support from a medical journal if a member the NARTC staff had acted as a judge in a Boehringer Ingelheim sponsored competition. Boehringer Ingelheim stated that it could not answer this allegation without further details. The editor of the journal had refused to be identified which was unfortunate, although understandable. The lack of evidence meant that the Panel was obliged to rule no breach of the Code in this regard.

The Panel examined the materials promoting the Respiratory ERC. These consisted of advertisements in the press, such as Practice Nurse (19 February and 21 May 1999) and Practice Manager (February 1999). One advertisement included an illustration of a Diploma of Higher Education in Respiratory Disease Management. Readers were asked to ring the Respiratory ERC for further information. The second advertisement referred to the modular courses and stated that educational grants were available for primary and secondary care. This advertisement stated that the Respiratory ERC was a charitable trust offering modular courses in respiratory care for health professionals. Neither advertisement referred to Boehringer Ingelheim.

A press release dated 27 January 1999 was provided by the Respiratory ERC. This referred to the nurse training programme. Reference was made to lung cancer and asthma although more emphasis was placed on COPD. The press release stated that the Respiratory ERC had received an educational grant from Boehringer Ingelheim. This was referred to as an initial grant with the expectation that the Respiratory ERC would be self financing within three years. The press briefing notes stated that Boehringer Ingelheim would have no direct input at any time into the educational material, content or running of the charity. The press release referred to 'A pioneering drive' and stated that the programme was designed to fill a 'therapeutic vacuum'. The press briefing stated that the '… flexibility in learning approach is unique'. A flyer which had been sent out gave details about the Respiratory ERC and the courses. There was no mention of Boehringer Ingelheim.

Paper copies of acetates used for health authority presentations were provided. One acetate gave details about the Respiratory ERC and stated that Boehringer Ingelheim had provided an educational grant to support the set up period. The next acetate gave details about the structure of the Respiratory ERC. The Panel noted that one of the seconded Boehringer Ingelheim staff played a key role in the organisation as Business Manager. As Business Manager she reported to the Chairman of the Trustees and had all of the five other members of staff, plus the regional facilitators, reporting in to her. The relevant staff were not identified as Boehringer Ingelheim employees.

A booklet entitled 'Diploma Programme', which was included in an information pack, stated that the Respiratory ERC '… was grateful for the help of a generous grant from Boehringer Ingelheim to set up the organisation and to the many other pharmaceutical companies that have offered their support since. The charitable structure of the Respiratory ERC has been designed to ensure that the only true beneficiary will be the respiratory patient…'.

The Panel first addressed whether the activities were subject to the Code. The Code applied to the promotion of medicines although there were certain clauses which had a more general application. The Panel considered that the COPD manual should have included more information about Boehringer Ingelheim's involvement than merely the fact that the company owned the copyright. The Panel considered that the company's sponsorship had not been made clear and a breach of Clause 9.9 of the Code was ruled. This was appealed by Boehringer Ingelheim.

The Panel considered that Boehringer Ingelheim was very much involved with the activities of the Respiratory ERC. It was doing more than providing a 'no strings attached' grant to establish the organisation. The company had considerable input to the day to day running of the Respiratory ERC. This was not necessarily unacceptable and there was no evidence that anything improper had occurred. The Panel was however concerned that the materials did not inform the reader of the major involvement of Boehringer Ingelheim in the establishing and running of the Respiratory ERC.

Given the extent of Boehringer Ingelheim's involvement, the Panel's view was that readers and those considering enrolling for the course should be aware of it. This should have been made a condition of sponsorship. Clause 9.9 of the Code referred only to the sponsorship of material relating to medicines. Some of the material did not mention medicines but some did. In the Panel's view all of the materials should have given details about Boehringer Ingelheim's involvement. The failure to do so meant that Boehringer Ingelheim had not maintained a high standard of conduct and a breach of Clause 9.1 of the Code was ruled. This was appealed by Boehringer Ingelheim.

The Panel noted that it had drawn Boehringer Ingelheim's attention to Clause 18.1 of the Code. There was limited information in this regard but the Panel considered that on the information available the training programme would enhance patient care and benefit the NHS. The training programme was not linked with the use of any medicine in particular. No breach of the Code was ruled in that regard.

The Panel noted that attention had also been drawn to Clause 2 of the Code which stated that activities or materials associated with promotion must never be such as to bring discredit upon or reduce confidence in the pharmaceutical industry. The Panel considered that given its ruling of a breach of Clause 9.1, the circumstances did not warrant a ruling of this clause which was reserved as a sign of particular censure. No breach of Clause 2 was ruled. This was appealed by the NARTC.

APPEAL BY BOEHRINGER INGELHEIM

Boehringer Ingelheim was disappointed that the Panel ruled breaches of Clauses 9.1 and 9.9 of the Code despite the fact that the Panel acknowledged that the activities concerned were not promotional, and, after careful deliberation, Boehringer Ingelheim had decided to appeal.

Clause 1.1 of the Code stated that the Code applied to the promotion of medicines. 'Promotion' was defined in Clause 1.2 as 'any activity undertaken by a pharmaceutical company or with its authority which promotes the prescription, supply, sale or administration of its medicines'.

Boehringer Ingelheim argued that this definition meant that the Code had no application to the activities concerned on two bases: firstly, the activity did not promote the prescription, supply, sale or administration of Boehringer Ingelheim's medicines; and secondly, it was not within Boehringer Ingelheim's authority to influence the materials produced due to the independence of the Respiratory ERC.

The company had to take issue with the observations made by the Panel concerning the relationship of Boehringer Ingelheim and the Respiratory ERC. It would argue in particular that the following passage was incorrect and did not reflect the evidence:

'The Panel considered that the Boehringer Ingelheim was very much involved with the activities of the Respiratory ERC. It was doing more than providing a 'no strings attached' grant to establish the organisation. The company had considerable input to the day to day running of the Respiratory ERC'.

This was simply not true. The fact was that the activities concerned were those of the Respiratory ERC and not Boehringer Ingelheim and therefore not covered by the Code.

Boehringer Ingelheim was concerned that to allow such statements to remain 'on the record' would provide ammunition to undermine the status of the Respiratory ERC.

A final practical problem was that the independent status of the Respiratory ERC meant that Boehringer Ingelheim was in no position to give the requested undertaking as to the future cessation of these activities.

Boehringer Ingelheim stated that the Respiratory ERC would be making comments on this factual issue.

Boehringer Ingelheim disagreed with the decision, having inferred that the activities were not promotional, to conclude that such non-promotional activities were, in any event, subject to Clauses 9.1 and 9.9 of the Code.

In accepting that Boehringer Ingelheim's activities were not promotional, the company would suggest that the Panel itself excluded the application of the Code. As stated above, Clause 1.2 of the Code defined 'promotion' as any activity 'which promotes the prescription, supply, sale or administration of its medicines'. As the activities did not promote Boehringer Ingelheim's medicines, then the Code had no application. This reiterated that Boehringer's Ingelheim's activities were outside the ambit of the Code generally and this provision in particular.

As to Clause 9.9, whilst there was no specific mention of promotion, Boehringer Ingelheim argued that the application of this provision was limited by Clauses 1.1 and 1.2 of the Code. Boehringer Ingelheim reiterated its contention that the general principle set out at the beginning of Clause 1.2 qualified the specific examples which followed, eg sponsorship.

In summary, Boehringer Ingelheim argued that it was not involved in the Respiratory ERC as suggested. The activities were not promotional and were hence outside the ambit of the Code in any event and it was not within Boehringer Ingelheim's authority to influence the materials produced, due to the independence of the Respiratory ERC.

The two Boehringer Ingelheim employees seconded to work for the Respiratory ERC in reality worked full time for the Respiratory ERC and not four days a week. The roles related to business development and marketing the courses. They were not involved in teaching or producing courses. The reporting line for academic matters was to the Trustees and not to the Boehringer Ingelheim seconded staff.

COMMENTS FROM THE RESPIRATORY ERC

The Respiratory ERC was very concerned about the case and strongly refuted all the allegations made by the NARTC. It provided detailed comments on all the matters raised by the NARTC. The Trustees of the Respiratory ERC were prepared to attend the appeal and respond to any questions from the Appeal Board. The Respiratory ERC stated that it received support from all the major pharmaceutical companies involved in respiratory medicine. The involvement of Boehringer Ingelheim, other than financial, was negligible. The establishing of the Respiratory ERC was covered in detail as were the roles and selection of the Trustees and the roles of the two staff seconded from Boehringer Ingelheim. The Respiratory ERC was willing for any interested parties to visit the organisation and to share with them details of the courses.

The Respiratory ERC commented that much education in the UK for healthcare professionals was

dependent on the pharmaceutical industry. The Respiratory ERC's view was that all income from industry to the charity should be declared in the accounts. In all its activities promoting courses or centres the Respiratory ERC had been entirely open about the structure of the organisation and the source of the initial financial support.

The Respiratory ERC was concerned that the details of this case were already in the public domain. It accepted that the disclosure had not come from the Authority.

APPEAL BY THE NATIONAL ASTHMA & RESPIRATORY TRAINING CENTRE (NARTC)

The NARTC stated that it had some additional information which contradicted some of the points made by Boehringer Ingelheim in its response. It was obviously disappointing that whilst the NARTC was open with both Boehringer Ingelheim and the Respiratory ERC, Boehringer Ingelheim had not been transparent with its funding arrangements and the Respiratory ERC had, for whatever reason, requested confidentiality for its response. Having considered this additional information, it might be felt that Clause 2 had been breached, particularly in the light of the misleading answers provided by Boehringer Ingelheim to the Panel.

Point 1

Boehringer Ingelheim admitted to having 'commercial and not entirely altruistic reasons'

The NARTC noted that Boehringer Ingelheim did not strenuously deny this, unlike many of its other answers, but stated that its staff could not recall this and no minutes from the meeting could be found. This statement was put to them clearly in a letter from the NARTC to which there was no response.

Point 2

Boehringer Ingelheim had set up the Respiratory ERC and had applied for and received charitable status for it

The NARTC was confused by Boehringer Ingelheim's response to this statement. In answer, Boehringer Ingelheim denied this allegation and stated that the Respiratory ERC paid all fees relating to the incorporation of the company. It also stated that the Charities Commission was fully aware of the funding provided by Boehringer Ingelheim to the Respiratory ERC to cover its set up and running costs.

It would therefore be appropriate to say that Boehringer Ingelheim had provided a large grant, ongoing support, training materials and staff to set up the Respiratory ERC.

Point 3

Boehringer Ingelheim had approached various opinion leaders with its course and offers of substantial funding

Point 4

Boehringer Ingelheim recruited the hospital

Whilst Boehringer Ingelheim strenuously denied these supposed allegations, the NARTC did not feel it was unreasonable to include these statements in its complaint. The NARTC agreed with the Panel that there was a difference between sponsoring an organisation by giving it a grant and having no further input, and providing a grant, ongoing support, training materials and staff, as in this case.

The NARTC provided a letter from a university professor which clearly implied that his department was approached by Boehringer Ingelheim at about that time, not that the chest physicians approached Boehringer Ingelheim in the autumn of 1997, as stated in Boehringer Ingelheim's response.

The NARTC understood that a consultant physician at a Manchester hospital was approached by Boehringer Ingelheim with the offer of funding to undertake the running/co-ordination of the Boehringer Ingelheim produced course in March/April 1998.

This made it clear that Boehringer Ingelheim produced the course itself and recruited hospitals with the offer of funding, prior to its staff starting work at the Respiratory ERC. It also appeared that Boehringer Ingelheim had misinformed the Authority about the date when one of the seconded staff started work at the Respiratory ERC.

Two of the consultants were 'targeted' because of their involvement in the BTS National Guidelines.

The NARTC did not state that the chest physicians were targeted because of their involvement in the BTS guidelines.

Point 5

That Boehringer Ingelheim owned the copyright for the Respiratory ERC's manual

Whilst the NARTC agreed that the training materials it had seen were of a good standard and represent a balanced view, there were some points the NARTC would see as placing undue emphasis on anticholinergics (Boehringer Ingelheim's key therapeutic area). In a final summary sheet provided, the final 'pay off' referred to anticholinergics whilst all other statements were broad. For example, there was no mention of how short acting beta agonists worked when they were recommended as first line before anticholingeric treatment.

Point 6

That brand names had been specifically avoided in the literature

As an educational establishment the NARTC considered that it was important for patient care that health professionals were aware of the brand as well as the generic name of a product. Whilst the prescription was likely to be written generically, patients often only referred to the brand name. If brand names were to be included this would mean that prescribing information about Boehringer Ingelheim's product would need to be included.

Point 10

Boehringer Ingelheim was intending to invest a large sum of money in the project

Boehringer Ingelheim, for whatever reason, still wished to keep this confidential at this stage. However, the NARTC was not incorrect in stating that it was a large sum as the Panel also noted that it was a large amount of support.

Point 11

That Boehringer Ingelheim was part-sponsoring health professionals to attend the Respiratory ERC's COPD module for which it owned the copyright

The NARTC noted that whilst Boehringer Ingelheim supported 180 course places during 1998, this was not all taken up and was therefore carried into 1999 and a small additional sum had been given by Boehringer Ingelheim to allow for increase in course costs since its original donation. When asked if it would be continuing to support a number of courses during 1999 (as it had done in previous years prior to the setting up of the Respiratory ERC), it did not respond to the NARTC's letter. It would be seen from its funding pattern (1996 – £19,500, 1997 – £18,800, 1998 – £30,600, 1999 – £1,045 (top up for 1998 course funding due to course fee increase)) that Boehringer Ingelheim had dramatically cut funding to the NARTC.

Point 12

That Boehringer Ingelheim proposed to withdraw financial support from a medical journal if a member of staff of the NARTC was used to judge a Boehringer Ingelheim competition

Whilst the NARTC knew that this was the case, unfortunately due to the commercial pressures within medical publishing those directly involved did not wish their names to be disclosed. This highlighted the power of the pharmaceutical industry budget when sponsorship for an award was under threat.

Point 13

Boehringer Ingelheim's advertising/PR agency had placed a number of advertisements in the medical press. The advertisements did not state Boehringer Ingelheim's involvement but the press release did

The NARTC was pleased that the Panel agreed that Boehringer Ingelheim's involvement was not clearly stated. The NARTC was again confused by Boehringer Ingelheim's response where it stated that it had not had any involvement in the placement of advertisements and did not believe the Respiratory ERC used the same PR agency as Boehringer Ingelheim. However, it stated that it referred the Respiratory ERC to a named PR agency. The NARTC contacted the PR agency which listed Boehringer Ingelheim as one of its clients. Interestingly the code at the bottom of the final page of the press release was Ld/bi/erc2/doc. Perhaps the PR agency could clarify if the 'bi' in this code stood for Boehringer Ingelheim and whether Boehringer Ingelheim was a client at the launch of this project Again it was unclear why Boehringer Ingelheim had not been more transparent about this arrangement.

This was an important point, as it would add to the fact that Boehringer Ingelheim had considerable involvement in the running of the Respiratory ERC and its activities.

Point 14

Respiratory ERC's launch campaign was driven by Boehringer Ingelheim

The complainants stated that once again the above points needed clarification. Did the PR agency also work for Boehringer Ingelheim; did the Respiratory ERC Business Manager who was a Boehringer Ingelheim employee act as the contact for the Respiratory ERC?

Clause 2

The complainants stated that Boehringer Ingelheim had clearly instigated the setting up of a course that directly competed with an existing course run by an independent charitable organisation. As a result health professionals had been put into an uncomfortable and confrontational position. This was supported by confidential correspondence from a health authority.

Through its activities Boehringer Ingelheim had: set up the Respiratory ERC; employed a medical education agency to write a training course under its copyright; given a large amount of funding to set up a rival charity; provided staff for the Respiratory ERC and involved key Boehringer Ingelheim personnel on the Board of Trustees.

Had it not carried out any of the above the NARTC would not have been involved in any of the problems with a health authority elsewhere which had previously always purchased courses from the NARTC. It was therefore the NARTC's belief that Boehringer Ingelheim had instigated activities which did not reflect well upon the pharmaceutical industry and, if disclosed, could bring the industry into disrepute. The NARTC hoped, therefore, that Clause 2 would also be ruled to have been breached.

RESPONSE FROM BOEHRINGER INGELHEIM

Boehringer Ingelheim said that it was most concerned that its original response must have been of insufficient detail to explain this difficult case and make absolutely clear the independent nature of the Respiratory ERC.

Introductory Paragraph 3 – Boehringer Ingelheim assumed that the NARTC's apparent concerns over the extent of the level of its sponsorship in the Respiratory ERC had been allayed in the Respiratory ERC's recent letter to the Authority, which gave full disclosure thereof. Boehringer Ingelheim reiterated that it had no authority over the Respiratory ERC and it was not appropriate for it to disclose financial information. Boehringer Ingelheim believed that any criticism to the contrary was unfounded.

Point 1 – In its original response, Boehringer Ingelheim had clearly confirmed that 'no-one asked has any recollection of this statement'.

The only additional point the company would like to make was that Boehringer Ingelheim was heavily involved in the area of respiratory medicine and was

concerned to promote its reputation as a company particularly committed in the field of respiratory healthcare and education.

Point 2 – Boehringer Ingelheim was unable to see the cause of the NARTC's confusion. The legal establishment of the Respiratory ERC as a company limited by a guarantee was carried out by the Respiratory ERC's lawyers without the involvement of Boehringer Ingelheim.

The subsequent funding level by Boehringer Ingelheim of the Respiratory ERC had been fully disclosed – this figure was far short of the £2 million suggested by the NARTC in its complaint. The provision of Boehringer Ingelheim's support to the Respiratory ERC was not contested, nor, it understood, was this problematic as far as the Authority was concerned.

Reference to approval by the Charities Commission was simply to indicate official endorsement of the fact that Boehringer Ingelheim's sponsorship of the Respiratory ERC was in good faith and did not prejudice the independence of the Respiratory ERC.

Points 3 and 4 – Boehringer Ingelheim freely acknowledged in its initial response that as part of its initial proposed project it approached sites in Reading, Manchester and Scotland. For various reasons that project proved impractical and it was important to note that the resultant project with the Respiratory ERC was very different to the one first considered.

As stated in the original response, the initiative in relation to the hospital which eventually led to the formation of the Respiratory ERC came from an unsolicited approach to Boehringer Ingelheim from that institution. This latter initiative was based on a wholly different model to the earlier project and its origins were unrelated.

Boehringer Ingelheim pointed out that the initial approach to it was made by two doctors in January 1998. As a result, two of Boehringer Ingelheim's employees participated in an informal meeting. This was followed by a further meeting at which Boehringer Ingelheim confirmed an interest in working together on a respiratory education project. As a result of the initial discussions Boehringer Ingelheim was invited to visit the hospital concerned in April 1998. As the university professor referred to by the NARTC was first involved in the third round of discussions, Boehringer Ingelheim respectfully suggested that this might explain why he thought at the time of writing the letter (May 1998) that the initial approach was made by Boehringer Ingelheim. Secondly, Boehringer Ingelheim was nevertheless pleased to note his confidence throughout the said letter as to Boehringer Ingelheim's commitment to education and sponsorship and his reasoned views as to the benefits of its sponsorship. In addition, Boehringer Ingelheim would like to bring the Authority's attention to the repeated statement by the professor regarding the independence of the Respiratory ERC. This applied equally now as it did then.

As to the approach to the consultant physician in Manchester, Boehringer Ingelheim repeated the observations above and those in its original response that this approach was freely admitted but was in relation to a wholly separate initiative. Likewise 'the course' referred to in the NARTC's observations on points 3 and 4 related to the earlier discontinued initiative rather than the subsequent initiative first proposed by the consultants involved with the Respiratory ERC.

As to the allegations that Boehringer Ingelheim misrepresented the date when one member of staff commenced her secondment at the Respiratory ERC, what was almost certainly said at the meeting in September 1998 was that she was to be seconded to the Respiratory ERC. It should be noted that there was no member of the NARTC present at the aforesaid meeting. Not unnaturally, the role of Respiratory ERC secondee was allocated several months prior to the actual commencement of duties. Boehringer Ingelheim denied that this demonstrated any economy with the truth as suggested by the NARTC.

Point 5 – Firstly, Boehringer Ingelheim did not understand how this new allegation by the NARTC related to the original issue raised hereunder, viz the copyright in the materials. Nevertheless, it pointed out that the final summary sheet like the rest of the training materials was developed without any input from Boehringer Ingelheim. It was independently edited and was further validated by a university and approved by the British Lung Foundation. Moreover, Boehringer Ingelheim reiterated that the course materials referred to related to only one of eleven courses run by the Respiratory ERC, the rest of which appeared to be unobjectionable to the NARTC.

Point 6 – Boehringer Ingelheim could do little more than reiterate the observations in its original response.

Point 10 – As stated above, Boehringer Ingelheim understood that the amount of support, which was not large, had been fully disclosed to the Authority by the Respiratory ERC.

Point 11 – Whilst Boehringer Ingelheim failed to appreciate the relevance of these observations, it reiterated its observations in its original response that the annualised level of grant had continued at a comparable level between 1996 and the present. The substantial uplifted amount paid in 1998 was effectively a pre-payment. As a direct consequence of the 1998 pre-payment, payments for 1999 had been reduced. However, Boehringer Ingelheim would like to point out that in 1999 year to date it had had £8,325 worth of the NARTC vouchers redeemed by customers and had another £7,650 worth of vouchers available for redemption, thus totalling £15,975. While it was not necessarily appropriate to combine these two it would be seen that this was a very different picture than presented in the appeal letter in which it was stated that the 1999 funding had been limited to £1,045. The implication was that this funding had been diverted to the Respiratory ERC. However, as a point of comparison, £9,180 worth of the Respiratory ERC vouchers had been redeemed in 1999 thus far.

Point 12 – Again Boehringer Ingelheim could only reiterate the observations made in its original

response. Moreover, it would point out that the judge for the competition was a trainer at that time for the NARTC.

Point 13 – Boehringer Ingelheim had responded to the material issues under this point in its original response.

Boehringer Ingelheim Corporate Public Relations (PR) was asked to advise on a suitable agency to assist the Respiratory ERC in its launch initiative. At the outset it should be emphasised that Corporate PR was distinct from product PR. Whereas the latter was committed to the promotion of products the former was committed to raising the profile of Boehringer Ingelheim as a corporation.

The PR agency in question was recommended and subsequent discussions led to Boehringer Ingelheim Corporate PR agreeing to jointly fund the launch initiative. Subsequent activities were conducted in the main between the PR agency and the Respiratory ERC. As mentioned, the role of Boehringer Ingelheim's Corporate PR was to raise the profile of Boehringer Ingelheim as a corporation, hence the inclusion of the company's name within the press release. An opportunity to achieve this was seen through publicising the company's support for a new initiative designed to improve the care of the respiratory patients over a wide range of respiratory diseases. The cost of the initiative was small, as could be seen on the invoice provided, clearly identifying the 50/50 split in costs and approved by a member of the company's Corporate PR Department. All materials produced were signed off as indicated on the approval form provided. Clearly 'bi' referred to Boehringer Ingelheim in its Corporate PR capacity.

Again the evidence was clear that Boehringer Ingelheim did not have 'considerable input' in the running of the activities of the Respiratory ERC as stated by the NARTC.

Point 14 – Boehringer Ingelheim denied this allegation. The first point was covered above. With regard to the second point, the PR agency's discussions were in the great majority directly with the Respiratory ERC. All materials were signed off by the Respiratory ERC, again as stated above.

Clause 2 – In relation to the NARTC's specific reasons why Clause 2 should be applicable to this case, Boehringer Ingelheim made the following comments:

1 As stated above, Boehringer Ingelheim did not set up 'a course'.

2 Boehringer Ingelheim was sure that the Respiratory ERC would argue that it was an independent charitable organisation in the same way as the NARTC.

3 As to the correspondence from a health authority, Boehringer Ingelheim could obviously make no comment as it had not been allowed to see it.

4 As to the repeated allegations in the bullet points and in the final paragraphs, Boehringer Ingelheim submitted that the points made both in this letter and in the company's original response, in conjunction with correspondence from the Respiratory ERC, put the Authority in full possession of the relevant facts and conclusively demonstrated that the NARTC had unfortunately misinterpreted information and incorrectly concluded a relationship that did not exist between Boehringer Ingelheim and the Respiratory ERC. This Boehringer Ingelheim denied as, it was sure, did the Respiratory ERC. The Respiratory ERC was totally independent of any influence from Boehringer Ingelheim and its activities, if looked at objectively, would be considered quite normal and acceptable within the industry.

Due to the seriousness of the comments made thus far in this case, the company would like to reiterate its protestations made in its own response to the original ruling:

1 The activities of Boehringer Ingelheim in relation to the Respiratory ERC were non-promotional and the company questioned the application of the Code in this case, Clauses 1.1 and 1.2 of the Code.

2 It was not within Boehringer Ingelheim's authority to influence the materials produced due to the independence of the Respiratory ERC. It hoped that with the evidence now available the Authority would be satisfied that the Respiratory ERC was totally independent of any influence of Boehringer Ingelheim. This was a fundamental point constantly stated and re-stated by Boehringer Ingelheim and the consultants who instigated and ran the Respiratory ERC.

3 Boehringer Ingelheim was particularly concerned regarding the statement in the original ruling: 'The Panel considered that Boehringer Ingelheim was very much involved with the activities of the Respiratory ERC. It was doing more than providing a 'no strings attached' grant to establish the organisation. The company had considerable input to the day to day running of the Respiratory ERC.'

Boehringer Ingelheim agreed with the Panel that this had been a difficult case due to the complexity, the time-scale involved and the different activities that were taking place at the time the Respiratory ERC was formed.

Regarding the different activities and having had a chance to read all the documentation again, Boehringer Ingelheim believed that some of the complaints referred to the original Boehringer Ingelheim concept relating to the formation of three centres and not to the very different final project which resulted in the formation of the Respiratory ERC.

It now hoped that, with the evidence in place, the complaints made had been disproved and that the Respiratory ERC could continue in its objective of improving education standards in respiratory medicine.

FURTHER COMMENTS FROM THE NARTC

The NARTC reiterated that it was Boehringer Ingelheim's role which it wished to challenge. The NARTC stood by its complaint and believed that there was a difference between sponsorship with no further input from the sponsor, compared to a sponsor producing and copyrighting materials, offering a large sum of money and providing ongoing support and staff.

The NARTC hoped that it could be agreed that Boehringer Ingelheim had driven and was very involved with this project. Two of Boehringer Ingelheim's staff were based at the Respiratory ERC, one of whom had a key role as business manager with a number of other staff reporting directly to her in this role. In addition, two of Boehringer Ingelheim's directors were Trustees of the Respiratory ERC. Boehringer Ingelheim's involvement in the launch of the Respiratory ERC was now apparent as a result of this complaint. Funding and activities were agreed and half funded by Boehringer Ingelheim's PR Department and the remaining funding signed off by a Boehringer Ingelheim employee at the Respiratory ERC.

The concept of the education resource centre project and its implementation by Boehringer Ingelheim had duplicated the existing activities of independent charities, reducing funding and future development and caused unnecessary difficulties between health professionals. Health authorities and individual purchasers had not been able to make an informed choice, as the level of Boehringer Ingelheim's involvement had not been transparent.

The number of health professionals who submitted sponsorship certificates from Boehringer Ingelheim for the NARTC COPD Course in 1998, prior to the launch of the Respiratory ERC, was 183. The number in 1999, post the Respiratory ERC launch, was 32, using funding from 1998. By funding its own project with a large amount of money, other charitable organisations were placed in a competitive situation. This inevitably led to greater spending on marketing using charitable money, which would be better spent furthering health professional education and patient care.

The NARTC would also like to draw to the Authority's attention that the NARTC had not disclosed the identity of the medical journal or its employee who stated that Boehringer Ingelheim had proposed to withdraw funding should the NARTC director be a judge. However, it was apparent from Boehringer Ingelheim's most recent response that it knew which journal and competition without that information being disclosed.

The NARTC asked the Appeal Board to stand by rulings on Clauses 9.1 and 9.9 of the Code and to consider that through its activities Boehringer Ingelheim had, in the view of many in the world of respiratory medicine, brought the industry into disrepute (Clause 2).

APPEAL BOARD RULING

The Appeal Board noted that the complaint concerned the activities of Boehringer Ingelheim. The activities of the Respiratory ERC did not come within the scope of the Code.

The Appeal Board was concerned that the Code had been used in what appeared to be a dispute between the NARTC and the Respiratory ERC.

The Appeal Board noted the submission that the Code had no application to the activities complained about as they did not come within the definition of promotion. The Appeal Board did not disagree with the Panel's view that, though the Code generally applied to the promotion of medicines, there were certain clauses which had a more general application.

With regard to the COPD Manual, the Appeal Board noted that the version used by the Respiratory ERC was a substantially redrafted version of the original which had been commissioned by Boehringer Ingelheim. The Appeal Board noted that Clause 9.9 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 supplementary information stated that the declaration of sponsorship must be sufficiently prominent to ensure that readers were aware of it at the outset. The Appeal Board considered that in the circumstances the involvement of Boehringer Ingelheim had been made sufficiently clear and no breach of Clause 9.9 of the Code was ruled. The appeal on this point was successful.

The Appeal Board noted the details of the relationship between the Respiratory ERC and Boehringer Ingelheim. It noted Boehringer Ingelheim's submission that it did not have a major involvement in either the formation of or the running of the Respiratory ERC. Boehringer Ingelheim had been approached and subsequently supported the formation of an independent charitable trust. The Respiratory ERC offered a wide range of respiratory education modules.

The Appeal Board did not accept that Boehringer Ingelheim would be unable to provide an undertaking as it would result in the Respiratory ERC having to make concessions regarding materials. An undertaking in these circumstances would not alter what had happened in the past but future sponsorship could be made conditional.

The Appeal Board considered that the relationship between the Respiratory ERC and Boehringer Ingelheim was not such that it needed to be declared in any more detail than had been done. No breach of Clause 9.1 was ruled. The appeal on this point was successful.

The Appeal Board then considered the appeal from the NARTC. The Appeal Board noted its rulings of no breach of Clauses 9.9 and 9.1 of the Code. It did not consider that there had been a breach of Clause 2 of the Code. The Appeal Board upheld the Panel's ruling of no breach of Clause 2. The appeal on this point was unsuccessful.

Complaint received **15 July 1999**

Case completed **27 January 2000**

CASE AUTH/914/8/99

MONMOUTH v MERCK SHARP & DOHME

Promotion of Vioxx

Monmouth submitted a complaint about a booklet, 'Vioxx Your Questions Answered', and a journal advertisement used by Merck Sharp & Dohme to promote Vioxx (rofecoxib).

Monmouth alleged that a section in the booklet was misleading and disparaging of its product Lodine (etodolac) as it attempted to establish Vioxx in one class of COX-2 selectivity whilst placing etodolac in another class along with agents that had been shown to have lower levels of COX-2 selectivity.

The Panel considered that this was a complex area. Given that this was a developing area of science it was necessary to be cautious when making claims to ensure that they were suitably qualified. In the Panel's view the first question and answer in the Vioxx booklet failed to adequately explain the basis on which the statements were made. The data for Vioxx had not been put into context of the data for the other medicines. The definition of COX-2 specificity had still to be universally agreed and so it was important in the meantime that readers were aware of the basis of any claims made. A breach of the Code was ruled. No breach was ruled with regard to an allegation that the section disparaged etodolac.

It was alleged that a claim in the booklet and the advertisement that Vioxx was the first agent to inhibit COX-2 but not COX-1 was untrue as etodolac was the first such agent since it had been available in the UK for 13 years longer than rofecoxib.

The Panel noted that in the human whole blood assay which it had submitted Merck Sharp & Dohme had provided evidence to indicate that rofecoxib did not inhibit COX-1 activity across its therapeutic range. The summary of product characteristics (SPC) stated that inhibition of COX-1 in humans had not been documented with any dose of Vioxx. The Panel noted Merck Sharp & Dohme's submission that the value of each test system should be taken into account when analysing results and that results in human whole blood assay were probably more representative than results using animal enzymes in an artificial setting.

The Panel considered that the claim that Vioxx was the first agent to inhibit COX-2 but not COX-1 was a broad claim. It was true to say that no COX-1 inhibition in humans had been documented. Vioxx and etodolac were similar when assayed in *in vitro* systems. Etodolac had been subjected to an *ex vivo* human whole blood assay but the Panel did not know if the results from this were such as to allow the medicine to be defined as COX-2 specific. On balance the Panel considered that the claim had not been adequately explained. The Panel considered that the claim was misleading in breach of the Code.

Monmouth alleged that Merck Sharp & Dohme had failed to provide substantiation following its request for an explanation of claims made in a booklet of abstracts presented and used at an international conference. In its response to Monmouth's request, Merck Sharp & Dohme had highlighted that the original paper was yet to be published, provided additional relevant publications and identified the appropriate sections of the SPC. The Panel noted that substantiation had been provided and no breach of the Code was ruled. On appeal by Monmouth, the Appeal Board considered that in the circumstances sufficient information had been provided. The appeal was thus unsuccessful.

Monmouth Pharmaceuticals Limited submitted a complaint about the promotion of Vioxx (rofecoxib) a non-steroidal anti-inflammatory drug (NSAID) by Merck Sharp & Dohme Limited. The complaint concerned claims which appeared in a booklet entitled 'Vioxx Your Questions Answered' (reference 05-00 VOX.99.GB.65129.B.35m.QO.599) and a journal advertisement (ref 05-00 Vox.99.GB.65289.Ja) which had appeared in Pulse, 21 August 1999.

Monmouth produced an NSAID, Lodine/Lodine SR (etodolac).

1 Alleged unbalanced and disparaging comparison of etodolac

COMPLAINT

Monmouth noted that the first question and answer in the promotional booklet 'Vioxx Your Questions Answered' was:

'VIOXX (rofecoxib) is the first agent to inhibit COX-2 but not COX-1. Aren't these already available in the UK?

No.

The activity of conventional non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and indomethacin is non-selective which means it inhibits both COX-1 and COX-2 at therapeutic doses. COX-2 preferential inhibitors such as meloxicam, nimesulide, etodolac and nabumetone have a greater inhibitory effect on COX-2 at therapeutic concentrations than on COX-1. VIOXX is a potent inhibitor of COX-2 but has no effect on COX-1. No inhibition of COX-1 in humans has been documented with any dose of VIOXX. VIOXX did not inhibit COX-1 at up to 80 times the starting dose (12.5mg) for osteoarthritis in healthy volunteers.'

In Monmouth's view this was a clear attempt to establish rofecoxib in one class of COX-2 selectivity whilst putting etodolac in another class along with agents that had been shown to have lower levels of COX-2 selectivity.

A comparison of the COX-2 selectivity data available for rofecoxib and etodolac where these agents had been studied in the Chinese hamster ovarian (CHO) model showed that rofecoxib had a >800-fold selectivity for COX-2 (Ehrich *et al* 1999) and etodolac had ~ 1,000-fold selectivity for COX-2 (Riendeau *et al* 1997). These CHO studies were conducted at the same centre and it was worth noting that the authors

of these papers used similar language to describe etodolac and rofecoxib. Similarly, in a direct comparison using the William Harvey Human Modified Whole Blood Assay (WHMA) and using IC_{80}s (the minimum concentration found to inhibit 80% of the COX-1 and COX-2 enzymes), rofecoxib was found to have a WHMA-COX-2/COX-1 ratio of <0.05 which represented >20-fold selectivity for COX-2. According to the same criteria, etodolac was found to have a ratio of 0.043 which represented 23-fold selectivity for COX-2 (Warner *et al* 1999).

By comparison, the COX-2 selectivity data available for nabumetone, meloxicam and nimesulide, where these agents had been studied in the same system, showed that in the CHO model meloxicam had a 300-fold selectivity for COX-2 whereas 6-MNA, the active metabolite of nabumetone, was found not to be selective for COX-2 (Riendeau *et al* 1997). In the WHMA meloxicam was found to have 11-fold selectivity for COX-2 (IC_{80} again) and nimesulide was found to have 6-fold selectivity for COX-2 (Warner *et al* 1999). The authors of this paper concluded that nabumetone was inactive and its active metabolite, 6-MNA, had no selectivity towards COX-2.

Monmouth could not see how these data justified the classification of etodolac as a preferential COX-2 inhibitor with other medicines such as meloxicam, nimesulide and nabumetone, whilst rofecoxib was classified in another category. This did not represent balanced or objective information. Not only was it unjustified to separate rofecoxib into a different category of COX-2 selectivity from etodolac but it was also disparaging of Monmouth's product, Lodine/Lodine SR, to link etodolac's level of COX-2 selectivity to those of agents which had been shown not to have as high a level of COX-2 selectivity as etodolac. Breaches of Clause 7.2 and 8.1 were alleged.

Monmouth noted that both etodolac and rofecoxib were described as selective inhibitors of COX-2 in their respective data sheet/summary of product characteristics (SPC).

RESPONSE

Merck Sharp & Dohme stated that etodolac was considered to be a preferential COX-2 inhibitor according to its data sheet. Therefore, within the promotional booklet 'Vioxx Your Questions Answered', classification of etodolac as a 'preferential' inhibitor of COX-2 reflected exactly the terminology used in the product's data sheet. This description was further supported by Pairet *et al* (1998), Hawkey *et al* (1999) and MIMS (August 1999). It was well recognised that different products in this class demonstrated different degrees of selectivity for COX-2. Merck Sharp & Dohme therefore did not understand how classification of etodolac as a preferential, or indeed selective, COX-2 inhibitor was disparaging. It therefore did not believe that the above description of etodolac breached Clauses 7.2 or 8.1 of the Code.

PANEL RULING

The Panel noted that COX-1 and COX-2 technology was a developing area of science. The supplementary information to Clause 7.2 headed 'emerging clinical or scientific opinion' stated that 'where a clinical or scientific issue exists which has not been resolved in favour of one generally accepted viewpoint, particular care must be taken to ensure that the issue is treated in a balanced manner in promotional material'.

The Panel noted that Brooks *et al* (1999) was a report of an international consensus meeting which sought to provide a definition of COX-2 specificity and to consider the clinical relevance of COX-2 specific agents. It was noted that the degree to which an NSAID inhibited the COX isoforms *in vitro* depended on the experimental assay used to assess enzyme inhibition; depending on the assay an agent's selectivity for COX-2 could vary 30-fold. It was recommended that results from *in vitro* be used only as a guide to the relative *in vivo* selectivity of different NSAIDs studied in the same assay system. It stated that the variety and variability of *in vitro* COX isoform assays and the unclear relationship between COX-2/COX-1 ratios obtained using *in vitro* assays led to the need for a new proposal to assess the effect of a medicine on COX isoforms. It was recommended that the 'human whole-blood assay be used to determine COX specificity'. It was stated that if a medicine inhibited COX-2 but not COX-1 across the entire therapeutic dose range using whole-blood assays it was COX-2 specific. It was noted that all currently available NSAIDs variably inhibited both isoforms in their therapeutic dose ranges and were therefore COX-1/COX-2 non-specific. Rofecoxib was defined as COX-2 specific. Etodolac was not mentioned by name in the report.

The Panel noted that the Vioxx SPC (dated June 1999) described it as a potent orally active COX-2 selective inhibitor within the clinical dose range and stated that inhibition of COX-1 in humans had not been documented with any dose of rofecoxib. It was noted that based on *in vitro* data inhibition of COX-1 might occur during chronic administration of Vioxx>250mg per day, 10 times the maximum recommended dose for osteoarthritis. The efficacy of Vioxx was stated to be due to its selective inhibition of COX-2.

The data sheet for etodolac (last reviewed in February 1997) stated that the inhibition of prostaglandin synthesis observed with etodolac differed from that of other NSAIDs. 'In an animal model at an established anti-inflammatory dose, cytoprotective PGE concentration in the gastric mucosa has been shown to be reduced to a lesser degree and for a shorter period with etodolac than with other NSAIDs. This finding is consistent with subsequent *in vitro* studies which have found etodolac to be selective for induced cyclo-oxygenase 2 (COX-2, associated with inflammation) over COX-1 (cytoprotective). Furthermore studies in human cell models have confirmed that etodolac is selective for the inhibition of COX-2. The clinical benefit of preferential COX-2 inhibition over COX-1 has yet to be proven.'

The Panel noted that Hawkey *et al* (1999) discussed COX-2 inhibitors as a new class of medicines and stated in a section headed COX-2 preferential inhibitors that 'etodolac … may be COX-2 selective but the evidence is less well-developed than for other drugs'. A section headed 'COX-2 agents' noted that

newer medicines were so much more selective than preferential inhibitors and stated that the term COX-2 specific inhibitor should be used to describe agents which inhibited COX-2 but had no effect on COX-1 over the whole range of doses used and concentrations achieved in clinical usage. Rofecoxib was noted within this class but it was also noted that many data were in abstract form only. Pairet *et al* (1998) also described etodolac as a preferential inhibitor of COX-2 using human whole blood assay.

Ehrich *et al* (1999) was a double-blind parallel group study which compared the analgesic efficacy of rofecoxib with placebo and ibuprofen in 102 healthy volunteers with dental pain and concluded *inter alia* that rofecoxib inhibited COX-2 without evidence of COX-1 inhibition.

The Panel considered that this was a complex area. Given that this was a developing area of science it was necessary to be cautious when making claims and to ensure that they were suitably qualified. There was a lack of consensus about how COX-1/COX-2 selectivity should be measured and expressed although the Panel noted that there had now been an attempt to reach agreement (Brooks *et al* 1999). The Panel noted that there had not been much time for debate of these recommendations. The Vioxx SPC described the product as selective whereas the Lodine data sheet described Lodine as being both selective and preferential. The Panel noted the allegation related to the classification of etodolac in one category and Vioxx in another. The Panel noted that results from *in vitro* studies (CHO model and the William Harvey Human Modified Whole Blood Assay) showed that etodolac and rofecoxib had a similar selectivity for COX-2 vs COX-1. According to a recent consensus on how COX-1/COX-2 selectivity should be measured and expressed (Brooks *et al* 1999), however, rofecoxib met the criteria that allowed it to be described as COX-2 specific ie in a human whole blood assay (*ex vivo*) it had been shown to inhibit COX-2, but not COX-1, across its entire therapeutic range. In this regard the Panel noted that the Vioxx SPC stated that 'Inhibition of COX-1 in humans has not been documented with any dose of Vioxx'. The Panel noted that the review by Pairet *et al* (1998) referred to a 1995 human whole blood assay on etodolac which showed that the medicine was a preferential inhibitor of COX-2. Despite the use of the term 'preferential' the Panel did not have the source paper to know if the assay had been such as to now allow etodolac to be described as COX-2 specific as defined in 1999 by Brooks *et al*.

In the Panel's view the first question and answer in the Vioxx booklet failed to adequately explain the basis on which the statements were made. The Panel did not consider that the paragraph at issue gave a balanced or fair reflection of the data. The data for Vioxx had not been put into context of the data for the other medicines. The definition of COX-2 specificity had still to be universally agreed and so it was important in the meantime that readers were aware of the basis of any claims made. A breach of Clause 7.2 was ruled.

The Panel did not consider the statement to be disparaging of etodolac as alleged and ruled no breach of Clause 8.1 of the Code.

2 Alleged untrue claim that Vioxx was the first agent to inhibit COX-2 but not COX-1

COMPLAINT

The claim that Vioxx was the first agent to inhibit COX-2 but not COX-1 was made in the booklet 'Vioxx Your Questions Answered' and in the journal advertisement which carried the headline 'The first agent to inhibit COX-2 but not COX-1'.

Monmouth stated that since ratios of selectivity for rofecoxib had been determined, it was clear that COX-1 inhibition by rofecoxib had been both detected and measured. These ratios were usually calculated from the minimum concentrations found to inhibit 50% of the COX-1 and COX-2 enzymes. In order to establish these ratios it was necessary for the agent being tested to provide 50% inhibition of both COX-1 and COX-2 enzymes. In several studies rofecoxib had inhibited both COX-1 and COX-2 by 50% and ratios for the COX-2 selectivity of rofecoxib had been determined. Clearly 50% inhibition of COX-1 was a very long way from the 0% inhibition of COX-1 implied by the claim 'The first agent to inhibit COX-2 but not COX-1'. In a publication sponsored by Merck Sharp & Dohme, for example, 42-fold selectivity for COX-2 had been reported for rofecoxib (Ford-Hutchinson 1993).

Monmouth stated that in a study by Warner *et al* (1999), rofecoxib was again found to be able to inhibit COX-1 by 50%. Furthermore there was a bar chart showing that at the concentration at which rofecoxib inhibited COX-2 by 80%, it inhibited COX-1 by 16%. The claims made in the promotional material and advertising for Vioxx seemed to be completely contrary to this finding. In this regard the Vioxx materials seemed to be in breach of Clauses 7.2, 7.3 and 7.8. It was worth noting that the authors of this paper chose to study COX-1 inhibition at the concentration which gave 80% inhibition of COX-2 because they thought this related to clinically relevant therapeutic levels of these agents. This was a wide-ranging study that compared 45 agents. There were two experimental compounds for which no COX-1 inhibition was detected at the concentration that gave 80% inhibition of COX-2, but rofecoxib was not one of these agents.

Monmouth considered that if the data cited above was sufficient to support a claim of inhibiting COX-2 but not COX-1, then etodolac was the first agent to inhibit COX-2 but not COX-1 since etodolac had been available in the UK for 13 years longer than rofecoxib.

RESPONSE

Merck Sharp & Dohme stated that the differential inhibition of the two COX isoforms was currently thought to be most accurately assessed by the human whole blood assay (Brooks *et al* 1999). In healthy human volunteers, rofecoxib demonstrated potent dose and concentration dependent inhibition of COX-2 activity *ex vivo* over a 5-1000mg single dose range, but did not inhibit COX-1 activity even at the highest (1000mg) dose tested. These data were reflected in the following statement contained within the SPC 'Inhibition of COX-1 in humans has not been

documented with any dose of Vioxx'. Ehrich *et al* (1999) provided details of the assays and utilised multiple sampling following single doses of Vioxx up to 1000mg. Schwartz *et al* (1999) used 12.5 and 25mg od for 6 days. Merck Sharp & Dohme was not aware that any comparable data showing no inhibition of COX-1 was available for any other UK licensed NSAID.

This view was supported by a report from the International Consensus Meeting on the Mode of Action of COX-2 Inhibition (ICMMAC) (Brooks *et al* 1999). The summary stated that 'All currently available NSAIDs variably inhibited both isoforms [of COX] in their therapeutic dose ranges and were therefore COX-1/COX-2 non-specific. In contrast, the newly developed agents, rofecoxib and celecoxib (not licenced in the UK), are COX-2 specific'. The definition of COX-2 specific being a medicine '...[T]hat inhibits COX-2 but not COX-1, across the therapeutic dose range, using the whole blood assays'.(emphasis added). In Merck Sharp & Dohme's view the claim was therefore completely supported by the available data and did not constitute a breach of the Code.

Merck Sharp & Dohme pointed out that Monmouth continued to dispute the above claim based not on results from human whole blood assays but on a variety of other assay systems. The variety and variability of *in vitro* COX isoform assays, and the unclear relationship between COX-2/COX-1 ratios, obtained using *in vitro* assays, and clinical outcomes had led to the recommendation of human whole blood assays for the determination of COX-2 specificity. The properties that made these assays the most appropriate assays to assess inhibition of COX-1 and COX-2 in the opinion of the authors included:

a) COX inhibition was assessed at therapeutically achievable medicine concentrations.

b) It involved clinically relevant target cells.

c) COX inhibition by active metabolites could be detected.

d) There was physiological protein binding.

e) Physiological pH, substrate concentrations applied.

f) With multiple samples pharmacokinetic influences could also be studied.

Merck Sharp & Dohme believed, together with a number of key opinion leaders in this field, that the *ex vivo* human whole blood assay was currently the most sophisticated and accurate method for assessing relative COX-2 selectivity. This assay technique involved administering the test medicine to healthy volunteers for a number of days. A blood sample was then taken and activity against COX-1 and COX-2 analysed to determine the selectivity of the medicine for COX-2 versus COX-1. This *ex vivo* technique was currently the most relevant means of measuring what was actually happening in the human body.

The William Harvey Research Institute Whole Blood Assay involved taking a blood sample from a healthy volunteer and then adding the test medicine to this sample. No test medicine was actually administered to the healthy volunteer. A number of variables were introduced by this methodology and the effects which would occur under normal clinical conditions in the human body were not as accurately mimicked. There were more limitations arising from this technique than a true *ex vivo* approach. With the Chinese hamster ovary cell assay, this was a much less sophisticated tool in terms of predicting COX-2 selectivity in man.

It was not surprising that there were variations in the measurement of COX-2 selectivity, depending on the assay method used to measure it. Monmouth had attempted to show that there was no real difference in the degree of COX-2 selectivity between its product and rofecoxib. However, for the reasons set out above, Merck Sharp & Dohme considered that this assertion in itself was a misleading argument.

Merck Sharp & Dohme considered that it had acted in good faith in asserting the benefits of the *ex vivo* human whole blood assay because it most accurately mimicked what was occurring in patients. It believed this to be wholly consistent with the statement in the SPC 'Inhibition of COX-1 in humans has not been documented with any dose of Vioxx'. In contrast Monmouth attempted to rely on 'surrogate' assays, whose limitations were well known and understood and had attempted to present data which ostensibly appeared to show little difference between the two products; however this was a reflection on the limitations of the assays, rather than a meaningful difference that could be demonstrated in humans.

Merck Sharp & Dohme therefore believed the above statement was based on an accurate, balanced and relevant representation of the data and therefore no breach of Clauses 7.3, 7.4 or 7.8 had occurred.

PANEL RULING

The Panel noted that in the human whole blood assay Merck Sharp & Dohme had submitted evidence to indicate that rofecoxib did not inhibit COX-1 activity across its therapeutic range. The SPC stated that inhibition of COX-1 in humans had not been documented with any dose of Vioxx. The Panel noted Merck Sharp & Dohme's comments about human whole blood assays. Pairet *et al* noted that the value of each test system should be taken into account when analysing results and that results in human whole blood assay were probably more representative than results using animal enzymes in an artificial setting.

The Panel referred to its comments at point 1 as to the complexity of the issue and the emerging scientific opinion in this area. The Panel considered that the claim Vioxx was the first agent to inhibit COX-2 but not COX-1 was a broad claim. It was true to say that no COX-1 inhibition in humans had been documented. As noted in point 1 above, Vioxx and etodolac were similar when assayed in *in vitro* systems. Etodolac had been subjected to an *ex vivo* human whole blood assay but the Panel did not know if the results from this were such as to allow the medicine to be defined as COX-2 specific. There had only recently been a consensus on the measurement and definition of COX-2 specificity. On balance the Panel considered that that claim had not be adequately explained. The Panel considered that the claim was misleading and ruled a breach of Clause 7.2 of the Code. The Panel considered that the allegations

of breaches of Clauses 7.3 and 7.8 were covered by these rulings.

The Panel noted that whilst Merck Sharp & Dohme had referred to Clause 7.4 in its response rather than Clause 7.2, it had nonetheless responded to the allegation.

3 Alleged failure to provide substantiation

COMPLAINT

Monmouth stated that it had written to Merck Sharp & Dohme requesting an explanation of claims made in an abstract published in a Vioxx promotional booklet 'Vioxx A collection of abstracts presented at EULAR [European League Against Rheumatism], June 6-11, 1999, Glasgow, Scotland'. One of the abstracts in this booklet (number 8; Schwartz *et al*) reported that the mean time-weighted average inhibition of thromboxane B_2 (vs baseline) was 9.0% and 5.1% for rofecoxib 12.5mg and 25mg. Monmouth noted that these values were different from 0, a sign of measurable inhibition of COX-1, and were obtained in humans at therapeutic doses. Monmouth did not know exactly how many volunteers were in each group but it seemed that they were all women.

Since placebo gave inhibition of –3.9%, the lowest recommended dose of rofecoxib differed from placebo by 12.9%. Monmouth could not see how the claim made by Merck Sharp & Dohme that 'Vioxx shows no inhibition of COX-1 in humans at therapeutic doses' could be reconciled with these data.

Monmouth requested further information from Merck Sharp & Dohme in order to give it the opportunity to explain this contradiction. It had not, however, supplied any further information – such as details of the statistical tests applied to the data – to substantiate its claims, which included '[rofecoxib] had no significant effect compared to placebo' and 'Among the active agents tested, [rofecoxib] was the only specific inhibitor of COX-2 without evidence of meaningful COX-1 inhibition'. Since the Code required companies promptly to provide substantiation upon request there was a breach of Clause 7.4.

Monmouth stated that it had pointed out to Merck Sharp & Dohme that since this request was for them to provide substantiation in relation to the validity of pharmacological claims (not in relation to the validity of indications approved in the marketing authorization), Clause 7.4 required the company to provide this substantiation Since six of the authors were listed as employees of Merck Sharp & Dohme, Monmouth could not see why it was unable to supply the information requested.

Monmouth added that the only other data cited by Merck Sharp & Dohme in support of its general claim 'Vioxx is the first agent to inhibit COX-2 but not COX-1' came from a study with only one comparator, indomethacin. In this study there were 16 volunteers from whom the rofecoxib data were obtained, all of whom were men. In contrast, the 9 volunteers from whom the indomethacin data were obtained were all women. Monmouth could not see that the data from this study was so compelling as to warrant dismissal of the COX-1 inhibitory properties of rofecoxib so clearly determined in the other studies to which it had referred.

Monmouth provided copies of correspondence on this subject published in The Lancet and The Pharmaceutical Journal.

RESPONSE

Merck Sharp & Dohme stated that it continued to be a little confused by the persistent allegation that it had failed to provide data to substantiate statements made in abstract 8 of the EULAR abstract booklet. Monmouth's letter of 24 June 1999 requested 'the original paper on which the abstract is based and any other comments you might consider useful'. In response Merck Sharp & Dohme highlighted that the original paper was yet to be published, provided additional relevant publications and identified the appropriate sections of the SPC in support of the statement. Indeed the data on file that would be provided on request to support this claim was a copy of the abstract in question that was presented at EULAR 99. Merck Sharp & Dohme did not believe this constituted a failure to provide substantiation and the allegation of a breach was completely unfounded.

Merck Sharp & Dohme wished to highlight that the EULAR abstract booklet was distributed exclusively at the EULAR 1999 meeting in Glasgow 6-11 June 1999. It was an international piece that had not been used as part of the UK promotional portfolio and its use was completely in accordance with the supplementary information for Clause 3 of the Code.

PANEL RULING

The Panel noted Merck Sharp & Dohme's submission that the EULAR abstract booklet had not been used as part of the UK promotional portfolio. The claim 'Vioxx shows no inhibition of COX-1 in humans at therapeutic doses' was not dissimilar to the SPC which stated 'Inhibition of COX-1 in humans has not been documented with any dose of Vioxx'.

Clause 7.4 of the Code required substantiation to be provided without delay at the request of members of the health professions. It could be argued that the company was not obliged to substantiate the claim as it had not been used in the promotion of the product. Nevertheless the Panel noted that Merck Sharp & Dohme had provided substantiation to Monmouth and no breach of Clause 7.4 was ruled.

APPEAL BY MONMOUTH

Monmouth stated that the claim that Merck Sharp & Dohme was asked to substantiate was that 'Vioxx shows no inhibition of COX-1 in humans at therapeutic doses'. This claim appeared in a variety of forms and in more than one promotional booklet, as illustrated in the original complaint. There was, however, clear evidence that rofecoxib did inhibit COX-1 in humans at therapeutic doses. Monmouth was not asking for a ruling that rofecoxib inhibited COX-1 in humans at therapeutic doses, merely that

Merck Sharp & Dohme had not substantiated its claim to the opposite.

Despite requests for Merck Sharp & Dohme to supply information about the data reported in the abstract in question, and to explain the contradiction between these data and the claims, it did not do so.

Furthermore Merck Sharp & Dohme had argued that the supplementary information to Clause 3 exempted it from having to provide substantiation. It had also repeatedly referred to statements made in the SPC for Vioxx. Neither of these approaches provided exemption in this instance.

Failure to provide substantiation

In the promotional booklet in question, abstract 8 presented values for COX-1 activity that were different from zero and were a sign of a measurable effect obtained in humans at therapeutic doses. Those figures confirmed a detectable level of COX-1 inhibition, which was in direct conflict with claims made by Merck Sharp & Dohme.

Monmouth thought this was a very important point and wrote to Merck Sharp & Dohme requesting a copy of the original paper and inviting comments that might explain the contradiction with its promotional claims. Merck Sharp & Dohme did not send Monmouth a copy of the original paper nor any explanation for the contradiction between these data and its claims for Vioxx. Neither had it provided the raw data nor the details of statistical tests applied to these data. The only information it sent Monmouth about this study was another copy of the abstract.

Monmouth's view was that it went against the spirit, as well as the letter, of the Code to publish claims of this sort in abstract form in a promotional booklet and then refuse to give details of the statistical methods and data behind the abstract. It should be remembered that some of the authors of the abstract were employees of Merck Sharp & Dohme and the company should have had access to the data.

As it was, Merck Sharp & Dohme had not – to date – responded to the central issue of providing the data behind the abstract and explaining how these data could be reconciled with its claim that Vioxx did not inhibit COX-1 in humans at therapeutic doses.

Clause 3: Promotion at international conferences

Monmouth stated that Merck Sharp & Dohme had argued that the supplementary information to Clause 3 relieved it of its responsibility to provide substantiation.

The supplementary information to Clause 3 concerned medicines which did not have a marketing authorization in the UK. The abstract booklet in question was distributed from a commercial exhibition stand in the UK when Vioxx had a marketing authorization in the UK. The supplementary information to Clause 3 did not, therefore, apply to this Vioxx promotional material.

Furthermore, Clause 3 was concerned with medicines which had been granted marketing authorizations in countries other than the UK. As far as Monmouth was aware, Vioxx had not at that time been granted a marketing authorization elsewhere in Europe. In other words, the supplementary information to Clause 3 was concerned with precisely the opposite situation to that which pertained in this case.

The booklet in question was issued at the EULAR meeting in Glasgow. It was freely available on the Merck Sharp & Dohme stand in the commercial exhibition held in association with the scientific meeting. Doctors from many European countries attended this meeting but by far the largest number were from the UK.

Merck Sharp & Dohme had submitted that this booklet had not been used as part of the UK promotional portfolio. Monmouth asked the Appeal Board to note, however, that the design style of the booklet was the same as the other UK promotional materials for Vioxx. It contained the same visual illustration and slogan 'TRUE ONCE-DAILY VIOXX' as the other UK promotional materials for Vioxx. It also referred to the product by its UK brand name.

The supplementary information to Clause 3 stated that any promotional material for medicines which did not have a UK marketing authorization must be clearly and prominently labelled as such. The promotional material in question was not labelled in this way.

This was clearly a piece of promotional material which was subject to the Code. As such, Merck Sharp & Dohme was required to provide substantiation for any information, claim or comparison (except in relation to the validity of indications approved in the marketing authorization, which was not the issue here).

Conflict with the SPC

Monmouth was also concerned that Merck Sharp & Dohme seemed to be trying to hide behind its SPC for Vioxx. Except in relation to the validity of indications, the Code did not permit this.

Monmouth noted that the figures for COX-1 inhibition given in the Schwartz *et al* abstract were averages. Since the lowest recommended dose of rofecoxib gave a mean COX-1 inhibition 12.9% greater than placebo, it was likely that in some volunteers the figure was higher. Monmouth knew that the SPC for Vioxx stated 'Inhibition of COX-1 in humans has not been documented with any dose of Vioxx'. This statement was clearly in conflict with the data presented in the abstract. The wording of the SPC, however, was a matter for the Medicines Control Agency and it might be that the wording of this section would now be reviewed.

Assessment of the data on COX-1 inhibition of rofecoxib

In its response, Merck Sharp & Dohme stated that the data on file to support the claim that Vioxx did not inhibit COX-1 in humans at therapeutic doses was a copy of the abstract in question. But this abstract reported data that showed the opposite of this claim.

The abstract, by Schwartz *et al*, reported that in humans at both of the recommended doses rofecoxib was found to inhibit COX-1. At the lower

recommended dose rofecoxib was found to inhibit COX-1 by 12.9% more than placebo. At the higher recommended dose rofecoxib was found to inhibit COX-1 by 9.0% more than placebo. These data did not, therefore, substantiate the claim that Vioxx did not inhibit COX-1 in humans at therapeutic doses.

Monmouth pointed out that the results were obtained from *ex vivo* assays of human whole blood taken from a total of 76 volunteers (with between 8 and 16 in each treatment group). This was the experimental approach that Merck Sharp & Dohme said it favoured and some of the authors of the abstract were employees of Merck & Co.

These results had been confirmed by Warner *et al* who studied 45 agents using the WHMA which these authors believed had advantages over other human whole blood assays. In this study the authors looked at the inhibition of COX-1 at the concentrations required to inhibit COX-2 by 80%. They calculated that this was a therapeutically relevant point at which to assess COX-1 inhibition. This also tied in closely with the 66.7% and 69.2% inhibition of COX-2 reported for the two recommended doses of rofecoxib by Schwartz *et al* in the abstract cited by Merck Sharp & Dohme.

Warner *et al* found that at this therapeutically relevant concentration, rofecoxib inhibited COX-1 by 16%. This further supported the view that rofecoxib did inhibit COX-1 in humans at therapeutic doses and underlined that Merck Sharp & Dohme had not substantiated the opposite.

Monmouth had studied the other material submitted by Merck Sharp & Dohme, including some general reviews around the subject of COX inhibition. It had also conducted literature searches of its own and amongst all of this it could find only one source of data showing a failure to find COX-1 inhibition by rofecoxib in humans. This was the paper by Ehrich *et al*.

This was an *ex vivo* assay using human whole blood. It differed from the work reported in the abstract by Schwartz *et al* in that a smaller total number of volunteers were used, there was only one active comparator (indomethacin), a wider range of rofecoxib doses was studied, single doses were used as opposed to dosing for six days and no COX-1 inhibition by rofecoxib was detected. The same marker for COX-1 was used in both of these studies, thromboxane TXB_2.

There was, however, another interesting difference between these two studies. All of the volunteers in the rofecoxib arm of the Ehrich *et al* study were men, compared with the volunteers in the indomethacin arm who were all women. All of the volunteers in the Schwartz *et al* study, which found rofecoxib to inhibit COX-1, were women. This raised the possibility that rofecoxib had a different COX-1 inhibition profile in men and women. Since more women than men were treated for osteoarthritis, the Schwartz *et al* data – showing COX-1 inhibition by rofecoxib – was more relevant to the majority of patients.

Monmouth believed that in a developing field, such as COX-1 inhibition, extreme caution should be exercised when interpreting the data from one particular study on its own. Monmouth believed that data from one study alone was not sufficient to support a promotional claim of this nature. The only data Monmouth could find in favour of Merck Sharp & Dohme's claim came from one study and ran against the trend established in other similar studies.

As there were data available that showed COX-1 inhibition in humans at therapeutic doses of rofecoxib, Monmouth concentrated on these data in its arguments above. Outside of the studies that had been conducted in humans at therapeutic doses, however, there was a general point that should also be considered. Rofecoxib had been shown to inhibit COX-1 by both 50% and 80% in various assay systems at various concentrations. From these data alone it could be concluded that it was highly likely that there was some inhibition of COX-1 in humans at therapeutic doses. Monmouth believed that any evidence to the contrary would have to be overwhelmingly convincing in order to substantiate a claim that rofecoxib did not inhibit COX-1 in humans at therapeutic doses. The assay systems used would have to be robustly confirmed with more than one marker consistently giving similar results when other workers repeated the experiments.

Summary

A proper assessment of the data available on rofecoxib's inhibition of COX-1 revealed that this agent had been shown to inhibit COX-1 in humans at therapeutic doses and that Merck Sharp & Dohme had not substantiated the opposite.

Monmouth believed that a closer examination of the supplementary information to Clause 3 showed that the promotional booklet in question was subject to the Code and that substantiation for the information, claims and comparisons in it should be provided upon request. It was not acceptable to refuse to supply this substantiation on the grounds that similar claims were made in the SPC. The substantiation should still be provided.

RESPONSE FROM MERCK SHARP & DOHME

Merck Sharp & Dohme said that before addressing what it believed to be the only substantiative issue arising out of the appeal, viz failure to provide substantiation on abstract 8 of the booklet of abstracts made available at EULAR 1999, it wished to clarify the process an appeal entailed.

In Monmouth's letter of appeal it did not confine itself to the above issue. Instead it broadened the allegation to failure to substantiate the claim 'Vioxx shows no inhibition of COX-1 in humans at therapeutic doses'. This was not raised in this form within the original complaint. Merck Sharp & Dohme's interpretation was that under the Constitution and Procedure for the Authority the appeal should be confined to the specific issue arising out of the abstract booklet.

The substance of the original allegation originally ran to approximately five paragraphs in Monmouth's initial letter of complaint. The appeal on this one point now ran to five pages. Merck Sharp & Dohme

believed Monmouth had used the appeal process to expand on its original complaint (of breach of Clause 7.4), as well as reiterating its concerns about the promotion of Vioxx *per se*. Merck Sharp & Dohme believed that this was an abuse of process and asked the Appeal Board to make a preliminary ruling as to what precisely was the subject matter of this appeal.

Merck Sharp & Dohme dealt in detail with what it believed to be the substance of the appeal, the allegation that it failed to provide adequate substantiation of data relating to abstract 8 in a booklet of abstracts available at EULAR 1999.

This abstract booklet was an international piece distributed exclusively at the EULAR 1999 meeting. It did not form part of the UK promotional portfolio for Vioxx.

The request for the original paper relating to this abstract could not be met as the full data had yet to be published in a peer reviewed journal. This was explained. As the next best alternative, a copy of the Ehrich paper was supplied. This reference provided relevant peer reviewed data relating to *ex vivo* assays and their role in determining relative COX-1/COX-2 inhibition, precisely the objective and content of abstract 8. As far as Merck Sharp & Dohme was concerned, Monmouth had requested the original paper and invited any comments Merck Sharp & Dohme might like to make. Merck Sharp & Dohme believed it had done that with its response.

To the best of Merck Sharp & Dohme's knowledge the first it knew of an allegation of failure to provide details of the statistical analysis was made by Monmouth in its letter of complaint.

Merck Sharp & Dohme believed that it had discharged its obligations to comply with Clause 7.4 and this was supported by correspondence to Monmouth which was provided.

Merck Sharp & Dohme's understanding of the effect of Clause 7.4 was to provide '… substantiation for any information, claim or comparison …'. It did not believe that it was the intention of Clause 7.4 to allow a competitor to embark on a fishing expedition to trawl for as much data as possible. In essence Monmouth's repeated requests fell into this latter category.

If Monmouth's appeal letter was taken at face value it seemed to Merck Sharp & Dohme to re-open all of the rulings including those to which it had already given the requisite undertakings. Merck Sharp & Dohme believed it was in the interests of all concerned to focus on the precise substance of this appeal.

FURTHER COMMENTS FROM MONMOUTH

Monmouth said that its appeal related to the third ruling of the Panel, namely on whether Merck Sharp & Dohme failed to provide substantiation when requested. In response to Monmouth's original complaint, Merck Sharp & Dohme sought to refute the allegation by saying that whilst it admitted not producing the original paper upon which the abstract was based, it had produced other information which it claimed did provide the substantiation required by Clause 7.4 of the Code.

In order to consider an appeal, it was necessary to test the substantiation which Merck Sharp & Dohme claimed to have provided. Monmouth noted that it now sought to exclude this on the basis that it was an 'abuse of process'.

Whilst Monmouth could see that it would be in Merck Sharp & Dohme's interest not to test its claims further, it could not be an abuse of process to examine matters Merck Sharp & Dohme itself put before the Panel in answer to the original complaint. Monmouth suggested that it was unnecessary, therefore, to trouble the Appeal Board with a preliminary ruling.

In summary: when Merck Sharp & Dohme was asked to provide substantiation for the information, claims and comparisons made in abstract 8 of the Vioxx promotional booklet at issue, it did not do so. It was, therefore, in breach of Clause 7.4 of the Code.

In addition to Monmouth's letter requesting the original paper on which the abstract was based, Monmouth wrote to Merck Sharp & Dohme pointing out that Monmouth had not received the substantiation requested and that Monmouth believed it to be in breach of the Code in this respect. In this letter it was pointed out that whilst the original paper had not been published Merck Sharp & Dohme should, where necessary, make unpublished data available to substantiate claims for its product and that this had not been sent to Monmouth. To this day Monmouth had still not seen the paper or data behind abstract 8 of the booklet in question.

In Monmouth's view Merck Sharp & Dohme had provided neither the substantiation requested nor a satisfactory explanation as to how its claims that Vioxx did not inhibit COX-1 in humans at therapeutic doses could be reconciled with the conflicting results summarised in abstract 8. Merck Sharp & Dohme did, however, send Monmouth other information. In the absence of the substantiation requested Monmouth did trawl through this other information and looked elsewhere to see if it could find such substantiation for itself. It could not.

Monmouth had always been concerned with the underlying validity of Merck Sharp & Dohme's claims for Vioxx and not just with scoring a narrow point on a detail of the Code. In June it asked Merck Sharp & Dohme to supply it with the paper behind abstract 8 because the figures in this abstract seemed to conflict with its general claims that Vioxx did not inhibit COX-1 in humans at therapeutic doses and with the statement in its SPC that COX-1 inhibition had not been documented in humans at any dose. Monmouth made it clear to Merck Sharp & Dohme at that time that this was the reason it was requesting this information.

Monmouth believed that Merck Sharp & Dohme was in breach of Clause 7.4 of the Code in two respects: both because it did not supply the paper or data behind abstract 8 when requested and because its claim that Vioxx did not inhibit COX-1 in humans at therapeutic doses could not be substantiated in the light of the figures given in abstract 8 and in the light of other data such as that from the study by Warner *et al.*

It was clear from a new Vioxx advertisement which had appeared since the Panel's initial rulings on this

case, that Merck Sharp & Dohme intended to continue making the claim that Vioxx did not inhibit COX-1 in humans at therapeutic doses. In support of this claim, which – though slightly differently worded – had the same flaws as before, it cited the Ehrich paper and omitted references to the data from the Warner paper and abstract 8 which conflicted with this.

APPEAL BOARD RULING

The Appeal Board noted that Monmouth had raised additional matters in its letter of appeal which had not formed part of the original allegation on this point. The Appeal Board considered that the only matter which it could consider was whether or not Merck Sharp & Dohme had provided substantiation in relation to abstract 8 of the EULAR booklet in accordance with Clause 7.4 of the Code.

The Appeal Board noted that the EULAR booklet was a collection of scientific abstracts which had been presented at the EULAR meeting in Glasgow. The cover sheets referred to Vioxx. The abstract booklet had not been produced by the UK company. It had been produced by the parent company and circulated only to attendees of the meeting. The UK company accepted that it was responsible for the booklet under the Code. The UK company had refused to allow it to be used in the UK promotion of Vioxx. The UK licence for Vioxx had been received a few days before the EULAR meeting.

The position was complicated because the abstracts had been presented within cover sheets promoting Vioxx. The only claim on the cover sheets was 'The Once-Daily Vioxx' and the statement 'Before prescribing please consult full physician circular'.

The Appeal Board noted Merck Sharp & Dohme's submission that the original paper had not yet been published. The company's representatives had stated that insofar as they were aware no drafts of the proposed paper were available; the most detailed information they could provide about the study by Schwartz *et al* was abstract 8 itself. The company had provided the complainant with two relevant additional references in response to the original request.

The Appeal Board considered that in the circumstances Merck Sharp & Dohme had provided sufficient information to Monmouth to support abstract 8. Monmouth's request had been for the original paper on which the abstract was based, but given that such did not exist the company was sent the abstract itself together with some supporting references. Reference had also been made by Merck Sharp & Dohme to supporting statements in the Vioxx SPC. The substantiation provided was in accordance with Clause 7.4. The Appeal Board upheld the Panel's ruling of no breach of Clause 7.4 of the Code.

The appeal was thus unsuccessful.

During its consideration of this case the Appeal Board was concerned that the EULAR booklet appeared not to meet the supplementary information to Clause 3 headed 'Promotion at international conferences'. The position had been complicated by the receipt of the marketing authorization immediately before the meeting which meant that the company could promote the product. The Appeal Board asked that Merck Sharp & Dohme be advised of its concern.

Complaint received **23 August 1999**

Case completed **27 January 2000**

CASE AUTH/919/8/99

SCHERING HEALTH CARE v GUERBET

Xenetix letter

Schering Health Care complained about a letter which a regional imaging specialist at Guerbet had sent to a hospital in relation to Xenetix, a Guerbet contrast medium. The letter followed earlier correspondence about contracts and prices and stated 'It should be noted that the contraindication for use in cases of known raised intracranial pressure has been removed from the data sheet. The MCA [Medicines Control Agency] has agreed that there should be no differentiation between the products of this type. This reasoning will also lead to the subsequent removal of the other contraindications'. The letter also stated 'I have also enclosed a sample request form should the department wish to evaluate Xenetix prior to making a decision.'

It was alleged by Schering Health Care that the letter was promotional and that it did not include the non-proprietary name adjacent to the most prominent display of the brand name. The letter should not have referred to the MCA. The statement about subsequent removal of other contraindications could be interpreted to mean that they were no longer valid and was alleged to be at best inaccurate and misleading.

The Panel noted that in the Code the term promotion did not include 'replies made in response to individual enquiries from members of the health professions or in response to specific communications whether of enquiry or comment, including letters published in professional journals, but only if they relate solely to the subject matter of the letter or enquiry, are accurate and do not mislead and are not promotional in nature.' The Panel noted that the hospital had asked Guerbet to confirm the variation to the Xenetix data sheet. The letter, written in response to this enquiry, stated that the contraindication for use in cases of known raised intracranial pressure had been removed from the data sheet but went on to state that there would be the subsequent removal of other contraindications. The letter also offered samples for evaluation. In the Panel's view the letter went beyond the scope of the original enquiry and the Panel queried whether the letter was accurate and not misleading. In the Panel's view the letter was subject to the Code.

The letter confirmed the removal from the data sheet of one specific contraindication and went on to state that there would be a subsequent removal of the other contraindications. The Panel considered that it was misleading and inappropriate to hint that there might be changes to the data sheet. Potential changes should not be mentioned. Only those that had been formally agreed could be mentioned. The Panel considered that the letter was thus misleading in breach of the Code. Although the letter referred to Xenetix the only mention of its active ingredients, iobitridol and iodine, was in the prescribing information on the back of the letter. A breach was ruled because this information was not provided adjacent to the most prominent display of the brand name which was on the front of the letter. A breach was also ruled because the Guerbet regional imaging specialist had failed to maintain a high standard of ethical conduct. No breach was ruled by the Panel with regard to the reference to the MCA. Upon appeal by Schering Health Care the Appeal Board considered that although reference to the MCA was not specifically prohibited by the Code, the spirit of the Code was such as to prohibit it unless such reference was required. A breach of the Code was ruled.

Schering Health Care Limited submitted a complaint about a letter written by a regional imaging specialist at Guerbet Laboratories Ltd to the chief pharmacy technician at a hospital. The letter, dated 1 June 1999, was headed 'RE: CONTRACT FOR CONTRAST MEDIA' and read:

'Following our submission of prices in regard of the above, I am writing to advise of the variation to product data sheet.

Variation to product data Sheet April 1999

It should be noted that the contraindication for use in cases of known raised intracranial pressure has been removed from the datasheet. The MCA [Medicines Control Agency] has agreed that there should be no differentiation between the products of this type. This reasoning will also lead to the subsequent removal of the other contraindications.

I have also enclosed a sample request form should the department wish to evaluate Xenetix prior to making a decision.'

COMPLAINT

Schering Health Care referred to Clause 1.2 of the Code which stated that the term promotion did not include 'factual, accurate, informative announcements… providing they included no product claims'. It believed this letter to be inaccurate and to exceed the basic information that would be acceptable under the definition. A factual announcement would not need to include a sample request form or the insupportable claim relating to the removal of the product's contraindications. These facts, along with the inclusion of both an indication (contrast media), a trade name (Xenetix), and the prescribing information for the product on the reverse of the letter, showed the letter to be overtly promotional in nature.

Schering Health Care alleged that the letter was a promotional item in breach of a number of clauses of the Code.

1 Clause 4.2 of the Code stated that the non-proprietary name of the medicine or a list of the active ingredients using approved names where such existed must appear immediately adjacent to the most prominent display of the brand name. As the brand name Xenetix only appeared once on the front of the letter, this must be the most prominent display and, as such, should have the non-proprietary name immediately adjacent. Schering Health Care alleged a breach of Clause 4.2.

2 Clause 9.4 stated that 'Promotional material must not include any reference to the Medicines Commission, the Committee on Safety of Medicines or the licensing authority, unless this is specifically required by the licensing authority.' The letter contained the sentence 'The MCA has agreed that there should be no differentiation between products of this type' and unless this was requested by the MCA it was in breach of Clause 9.4 of the Code.

3 The paragraph of the letter headed 'Variation to product data Sheet April 1999' advised of the removal of a single contraindication from the data sheet after an apparent agreement by the MCA that there should be no differentiation between products of a certain type with respect to that particular issue. It then made the claim that 'This reasoning will also lead to the subsequent removal of the other contraindications'.

It was unclear exactly what was meant by this, but it could be interpreted as a statement that the product's remaining contraindications were no longer valid and would be removed from the data sheet. This was at best inaccurate and misleading and, at worst, could have grave safety implications if it led to the administration of the product to a patient with any of the number of contraindications still listed in the prescribing information on the reverse of the letter.

Schering Health Care alleged that the distribution of this inaccurate and misleading information constituted a breach of Clause 7.2 of the Code. It also believed that due to the potentially serious nature of this inaccurate information the Panel might wish to consider whether there had been a breach of Clause 15.2 or Clause 2. This type of promotion was of questionable ethical standing and could be seen as bringing discredit upon, or a reduction of confidence in, the pharmaceutical industry.

RESPONSE

Guerbet stated that on 20 January 1999, it received a letter dated 18 January from the pharmacy department of an NHS Trust hospital, signed by a chief technician, inviting Guerbet to tender for supplies of contrast media. A copy of this letter was provided. A regional imaging specialist at Guerbet responded to the request in a letter headed 'Strictly private & confidential' and dated as received on 28 January 1999. A copy of this letter was provided.

Due to the internal decision making process within the NHS Trust, it took some time for the contract to be considered. During this period, Guerbet varied the Xenetix product information. An employee of the NHS Trust subsequently spoke to Guerbet by telephone and asked it to confirm the variation about the Xenetix product information. The letter complained of by Schering Health Care was the letter sent by the regional imaging specialist to an employee of the NHS Trust in response to this telephone request.

Guerbet pointed out that certain areas of the letter submitted to the Authority by Schering Health Care had been blanked out, including the heading, which read 'Strictly private & confidential'. Guerbet expressed concerns about how the letter had come into Schering Health Care's possession and the company's acceptance and use of a commercially sensitive letter. Guerbet pointed out that this complaint raised serious issues of a delicate nature and listed those which would necessarily have to be brought into the public domain if an investigation took place. The company suggested that in the light of the sensitive nature of the explanation provided above, any public consideration of this complaint would not benefit the NHS Trust or Schering Health Care and it was not in the interest of the Authority, the NHS Trust or Schering Health Care to continue with it.

Guerbet submitted that the letter was not promotional and thus the complaint could not be substantiated by Schering Health Care. Although it was not accepted by Guerbet that the letter was promotional, each of the points raised by Schering Health Care were addressed as follows in turn:

Guerbet pointed out that it was a requirement of the Code (Clause 17) that a sample request form must be provided if an evaluation was required.

It was accepted by Guerbet that it was debatable that the sentence 'The MCA has agreed that there should be no differentiation between products of this type' should have been written by the Guerbet employee. Guerbet wished to emphasise that this was a comment offered by the employee that speculated on the outcome of a decision by the MCA.

Guerbet referred to the paragraph headed 'Variation to product data Sheet April 1999' and pointed out that the paragraph heading was factually correct.

Although the letter was not promotional, Guerbet was willing to concede that if it was, both the second and third sentences should not have been written. Guerbet had had discussions with the MCA over this issue, and Guerbet's employee had made statements that, if the letter were promotional material, would have breached the Code. In relation to the third sentence, Guerbet asked that the actual wording as complained of by Schering Health Care was taken into account. First, Schering Health Care had stated that it was not sure what the entire paragraph meant. Second, Schering Health Care then sought to interpret the contents of the paragraph in a way that best illustrated its argument. Finally, it was pertinent to point out that the sentence referred to 'the subsequent removal…'. The use of the word 'subsequent' referred to something that would follow on at a later time or date and did not refer to the present. At best this statement could be described as made in error, not as a misleading comment.

If this letter was promotional material, which it was not, Guerbet accepted that there was a potential for the company to have breached Clause 15.2 or Clause 2 of the Code.

Guerbet took the comments made by its employee seriously, and had initiated procedures to avoid a similar incident in the future.

Taking the context of this letter into account, Guerbet argued that the letter was not promotional, as described by Schering Health Care and in consequence, Guerbet had not broken the Code. Where it was accepted by Guerbet that some

comments made in the letter, if it was of a promotional nature, should not have been made, procedures had been put in place to help prevent a repeat of the matters complained of by Schering Health Care.

Guerbet invited the Director to consider that the letter was not promotional and dismiss the complaint accordingly.

PANEL RULING

The Panel noted Guerbet's suggestion that the complaint be withdrawn but also noted that Paragraph 14.1 of the Constitution and Procedure only allowed complaints to be withdrawn by the complainant with the consent of the respondent until such time as the respondent's comments on the complaint had been received by the Authority, and not thereafter. This had not happened so the Authority was obliged to deal with the complaint.

The Panel noted that a chief hospital pharmacy technician had written to a regional imaging specialist at Guerbet on 18 January 1999 notifying the company that as the hospital's present contract for contrast media was due to expire at the end of February it was now inviting companies to submit prices for the full range of products detailed for a one and two year contract. When submitting the quotation the company was asked to specify the unit price per vial/bottle, the pricing structure and delivery charge. The information was requested by 9 February 1999. Guerbet responded via a letter headed 'Contract for contrast media' which provided details about its non-ionic contrast medium, Xenetix, with regard to its strength, and the company's arrangements for a 24-48hr delivery service and after sales support service. Hospital price lists and product literature were provided. The Panel noted that in April 1999, before the hospital had made a decision about the contract, the Xenetix product data sheet was varied. Guerbet advised the hospital of this variation at its request via the letter which was the subject of this complaint.

The Panel noted that Clause 1.2 of the Code stated that the term promotion did not include 'replies made in response to individual enquiries from members of the health professions or in response to specific communications whether of enquiry or comment, including letters published in professional journals, but only if they relate solely to the subject matter of the letter or enquiry, are accurate and do not mislead and are not promotional in nature.'

The Panel had first to decide whether or not the letter was subject to the Code. The Panel noted that a hospital employee had asked Guerbet to confirm the variation to the Xenetix data sheet. The Panel noted that the letter, written in response to this enquiry, stated that the contraindication for use in cases of known raised intracranial pressure had been removed from the data sheet but went on to state that there would be the subsequent removal of other contraindications. The letter also offered samples for evaluation. In the Panel's view the letter went beyond the scope of the original enquiry and the Panel queried whether the letter was accurate and not misleading. In the Panel's view the letter was subject to the Code. It was immaterial that the letter had been headed 'Strictly private and confidential'.

The Panel noted that the letter confirmed the removal from the data sheet of one specific contraindication and went on to state that there would be a subsequent removal of the other contraindications. The Panel considered that it was misleading and inappropriate to hint that there might be changes to the data sheet. Potential changes should not be mentioned. Only those that had been formally agreed could be mentioned. The Panel considered that the letter was thus misleading in breach of Clause 7.2 of the Code.

The Panel noted that although the letter referred to Xenetix the only mention of its active ingredients, iobitridol and iodine, was in the prescribing information on the back of the letter.

The Panel noted that Clause 4.2 of the Code listed the component parts of the prescribing information and, in addition, stated that the non-proprietary name or a list of active ingredients must appear immediately adjacent to the most prominent display of the brand name in not less than 10 point bold or in a type size which occupied a total area no less than that taken by the brand name. Clause 4.1 of the Code stated that the information listed in Clause 4.2 must be provided. Failure to do so would therefore be a breach of this clause and not of Clause 4.2. The failure to include the non-proprietary name immediately adjacent to the most prominent display of the brand name, which in the Panel's view was in the body of the letter, meant that Guerbet had not complied with Clause 4.1. The Panel therefore ruled a breach of Clause 4.1 of the Code.

Clause 9.4 prohibited references to three specific bodies, the Medicines Commission, the Committee on Safety of Medicines and the licensing authority, unless such reference was specifically required by the licensing authority. The Panel noted, therefore, that reference to the MCA was not prohibited by this clause. The licensing authority was a statutory concept defined in Section 6 of the Medicines Act 1968 and comprised the health ministers and agricultural ministers. The MCA acted on behalf of the licensing authority but was not the licensing authority. The Panel noted that the letter referred to the MCA and not to the licensing authority. No breach of Clause 9.4 was ruled.

The Panel considered that in relation to the requirements of the Code, the regional imaging specialist, by writing the letter, had failed to maintain a high standard of ethical conduct and comply with all the relevant requirements of the Code. A breach of Clause 15.2 was ruled. The Panel did not consider that the letter was such as to bring discredit upon, or reduce confidence in the pharmaceutical industry and ruled no breach of Clause 2 of the Code.

During its consideration of this case the Panel also noted that the prescribing information for Xenetix did not include the legal classification of the product or its cost as required by Clause 4.2 of the Code. The Panel requested that this be brought to Guerbet's attention.

The offer to provide an after sales service to include, *inter alia*, sponsorship of meetings and medical books was taken up with Guerbet under the provisions of

Paragraph 16 of the Constitution and Procedure (Case AUTH/959/11/99).

APPEAL BY SCHERING HEALTH CARE

Schering Health Care appealed the Panel's ruling of no breach of Clause 9.4 with regard to the reference in the letter to the MCA. Schering Health Care stated that the Panel had interpreted the Code in a strict and irrational manner on the basis of a line of argument which was not even advanced by Guerbet. According to the introduction to the Code it was a condition of membership of the ABPI that companies 'abide by the Code in both the spirit and the letter'. Schering Health Care suggested that this principle applied also to the interpretation of the Code by the Panel.

As the Panel indicated, Clause 9.4 did not expressly refer to the MCA but Schering Health Care contended that the MCA, while acting for the licensing authority, was the agent of the licensing authority. As a consequence reference to it was equivalent to reference to the licensing authority. Also, the MCA was generally perceived by doctors and other relevant professionals as being the *de facto* licensing authority.

Although the MCA was generally viewed, in practice, as acting as the licensing authority, the Panel argued that this body could be mentioned by name but not the health ministers as a whole (see below). The CSM and the Medicines Commission, however, although they were seen as more independent of the licensing authority, could not be mentioned. Schering Health Care could not see the logic in this argument.

The reasoning of the Panel would have the anomalous effect that promotional material could refer to the UK health ministers, or any of them, alone, but not the UK health ministers and the agricultural ministers together. It was not clear from the ruling whether it was forbidden to use the expression 'licensing authority' or whether it was merely forbidden to refer to the UK health and agricultural ministers. The latter proposition appeared to be the logical conclusion from the ruling, which was somewhat irrational.

Schering Health Care suggested that the Panel had failed to take any account of the overriding reason for the existence of Clause 9.4. As Schering Health Care understood it, the aim was to prevent companies seeking to appropriate regulatory bodies to assist with the promotion of specific products. The clause ensured a clear separation between the commercial activity of companies and the public health functions of the regulatory bodies, in a manner which sought to preserve public confidence in the impartiality and objectivity of the public bodies. Unless Schering Health Care was mistaken in its understanding, the ruling completely undermined this principle and the logical conclusion was that Clause 9.4 should be removed.

Schering Health Care proposed to seek the views of the MCA to the ruling and it would hope to have its response before the appeal hearing.

RESPONSE FROM GUERBET

Guerbet did not comment on the reasons for the appeal given by Schering Health Care.

FURTHER COMMENTS

Schering Health Care submitted the views of the MCA on the matter. The MCA stated that the Medicines (Advertising) Regulations 1994, as amended, did not prohibit the mention of the MCA or the licensing authority in advertisements aimed wholly or mainly at persons qualified to prescribe or supply, though such a reference could be misleading in certain circumstances. The administration of the Code was, of course, the remit of the Authority.

APPEAL BOARD RULING

The Appeal Board considered that although the MCA was not specifically mentioned in Clause 9.4 the term 'licensing authority' was, in practice, interpreted to mean the MCA. Thus, in its view, the spirit of Clause 9.4 prohibited any reference to the MCA unless this was specifically required. A breach of Clause 9.4 was therefore ruled.

The appeal was thus successful.

During its consideration of this case the Appeal Board considered that the next edition of the Code should be amended such that the MCA was specified in Clause 9.4.

Complaint received **31 August 1999**

Case completed **10 February 2000**

CASE AUTH/927/9/99

PHARMACEUTICAL ADVISER v ASTRAZENECA

Educational meeting

A pharmaceutical adviser from a medical centre complained about what an independent speaker had said at an educational meeting held at the medical centre and sponsored by AstraZeneca. The doctors at the medical centre had been high users of AstraZeneca's product Losec (omeprazole) but had recently, in collaboration with the complainant, reviewed their use of proton pump inhibitors (PPIs) and decided to use a maintenance dose of Zoton (lansoprazole) where appropriate. The complainant stated that the speaker's opening remarks included disparaging comments about pharmacists and called into question their suitability to advise GPs on prescribing matters. The presentation was unbalanced and generally disparaged Zoton with a definite bias towards presenting negative studies. The complainant listed a number of areas where the available evidence regarding Zoton was misrepresented. The complainant stated that the meeting was disguised promotion and that its objective seemed to be to undermine the work of pharmaceutical advisers.

The Panel examined the slides which the speaker had used and decided that some of the comparisons presented were unfair and misleading. In addition the material disparaged Zoton. Breaches of the Code were ruled which were appealed by AstraZeneca. No breach of the Code was ruled with regard to data presented about an interaction between Zoton and food.

The Panel was concerned that the letter of invitation to the meeting gave the impression that it was an educational meeting and that only the lunch was sponsored by AstraZeneca; in fact the whole meeting had been sponsored by the company and the Panel considered that it was in effect a promotional activity which had been disguised. A breach of the Code was ruled.

With regard to the allegation that the speaker disparaged pharmacists, the Panel noted that the parties' accounts differed. There was no way of knowing what had been said and so no breach of the Code was ruled. This was appealed by the complainant.

Upon appeal by AstraZeneca regarding the content of the presentation, the Appeal Board appreciated the difficulties for companies asking independent speakers to present at such meetings. It would be unsatisfactory for companies to dictate to speakers what they should present. Nevertheless, depending on their degree of involvement in the meetings, companies might have to ensure compliance with the Code. If this were not so then companies could employ independent experts to say what they, as companies, could not. No judgement would be made with regard to the professional integrity of a speaker. It was not a question of what a speaker said, it was a question of whether it was appropriate for the company to have sponsored the presentation.

Overall the Appeal Board considered that given AstraZeneca's involvement with the meeting, it was responsible for what the speaker said. The speaker was known to AstraZeneca, his attendance at the meeting had been facilitated by the company and he had been briefed as to the objective of the meeting. The Appeal Board considered that the meeting was promotional. The Appeal Board noted AstraZeneca's submission that the content of the slide and accompanying verbal comments from the speaker should be taken as a whole rather than assessing the slide content alone. The Appeal Board considered that the comparisons of Zoton and Losec in the slides, irrespective of any verbal comment, were misleading and unfair as alleged. The Panel's rulings were upheld.

With regard to the complainant's appeal concerning the allegation that the speaker disparaged pharmacists, the Appeal Board noted the differences between the parties' accounts; it was thus impossible to tell where the truth lay. The Appeal Board considered, however, that should disparagement have occurred then AstraZeneca could not be held responsible for it. The company would have known the speaker's views with regard to the use of PPIs but it had no reason to believe that he would disparage pharmacists – if indeed he did. Companies could not be held responsible for chance remarks made by speakers at meetings they had sponsored. The Panel's ruling of no breach of the Code was upheld.

COMPLAINT

A pharmaceutical adviser at a medical centre complained about a meeting organised by AstraZeneca.

The complainant stated that a local AstraZeneca representative organised a sponsored educational meeting at the medical centre which was attended by the doctors from the centre plus other GPs in the locality.

The complainant could not recall the exact title of the presentation but it made reference to a 'roller-coaster' with the implication that the main thrust of the talk would be the cyclical nature of gastro-oesophageal reflux disease. The talk was given by a hospital consultant.

This group practice, like many locally, was a high user of proton pump inhibitors (PPIs). AstraZeneca's product Losec (omeprazole) was almost exclusively used for conditions where PPIs were indicated.

The complainant stated that one of her main tasks at the medical centre, as agreed with the partners, was to review all patients prescribed PPIs with a particular remit to review those patients where use of a maintenance (half dose) PPI might be appropriate (these patients were generally 'dyspeptics' and those with mild reflux disease). Stepping down to a maintenance dose of acid suppressant agent was the approach advocated by the British Society of

Gastroenterology. After an independent review of the literature, it was decided to use the licensed maintenance dose of an alternative PPI, Wyeth Laboratories' product Zoton (lansoprazole). The financial implications of this review were, of course, obvious. It would be to the benefit of the prescribing budget and therefore the local population (as it might free up resources), and to the detriment of AstraZeneca.

The complainant stated that the speaker's opening remarks included several disparaging comments about pharmacists and called into question their educational achievements and suitability to advise GPs on matters of prescribing (the speaker was unaware that there was a pharmacist in the audience). The body of the presentation generally comprised a 'character assassination' of Zoton and although the speaker presented published work, a definite bias towards presenting negative lansoprazole studies was evident. The talk was delivered in a manner and at a pace that made it impossible to interject when what the complainant believed to be spurious evidence was presented. The speaker's manner was patronising and the main objective of his talk appeared to be scare-mongering. In the complainant's view overall the content of the presentation did not reflect its title. It seemed that the content of the presentation might have been influenced by AstraZeneca and was specifically intended to undermine the complainant's work and that of other advisers working with general practitioners. During a subsequent private conversation with the speaker the complainant discovered he was ill informed in a number of areas and he was, in one-to-one conversation, prepared to accept this fact. Unfortunately, the GPs in the audience had already left, possibly with a biased opinion from the respected authority and there was no opportunity to redress the balance due to the limited time available.

The complainant discovered later that AstraZeneca had arranged for this speaker to present that evening in another neighbouring health authority which had similarly chosen to use a competitor's product.

The complainant alleged that the speaker's presentation was in breach of Clause 7.2 of the Code. The speaker chose to disregard several pieces of research that would have brought balance to his presentation. In fact, during their conversation the speaker showed the complainant a Medline search that he had conducted which contained abstracts of several positive lansoprazole trials that he had failed to mention in his presentation. Areas of particular note where the body of available evidence was misrepresented to the benefit of AstraZeneca included:

- Trials of comparative efficacy.

- Adverse drug reaction rate data were presented that suggested that the rate of diarrhoea in particular was twice as high in patients treated with lansoprazole compared with omeprazole. However, data from prospective trials that indicated that there was no significant difference in the adverse drug reaction (ADR) rate between the two medicines was not presented.

- Effect of food on the bioavailability and efficacy of lansoprazole – recent trial work, suggesting that the timing of the lansoprazole dose (in relation to food) was in fact irrelevant with repeated dosing, was not mentioned.

- Price comparisons – the speaker made reference to the fact that high dose generic ranitidine (ie 300mg bd) was significantly cheaper than half-dose PPI (which it was not, comparative costs being £35.12 and £14.21 respectively). He questioned why anyone would want to follow such a strategy. During the subsequent conversation with the complainant the speaker agreed that he had clearly been misinformed regarding generic prices. Unfortunately few GPs were aware of comparative costs and would have accepted this information without question. He subsequently accepted that he had been wrong in these assumptions and could therefore see some justification for the practice's actions.

- Interactions – the speaker suggested that lansoprazole was subject to a greater number of drug interactions than omeprazole. The complainant found this claim completely unacceptable. For example, Hansten and Horn's Drug Interactions Analysis and Management listed 43 drug-drug interactions attributable to omeprazole and only 23 to lansoprazole. A recent independent review of drug-PPI interactions concluded '..omeprazole, lansoprazole and pantoprazole are structurally very similar and an evaluation of available data indicate that they demonstrate generally very similar properties with respect to metabolism and interactions'.

The complainant referred to Clause 8.2 of the Code that 'The health professions and the clinical and scientific opinions of health professionals must not be disparaged'.

The speaker was unaware there was a pharmacist in the audience. The complainant paraphrased one of his opening comments as she could not recall the exact wording 'I find it unbelievable that pharmacists are being allowed to tell us, the people with four grade A 'A' levels, what to do'. The complainant found this comment most offensive, especially in the context of what the presentation had purported to be about and suspected that the AstraZeneca representative had fuelled this comment by informing him that a pharmacist had been involved in the stepping down of patients onto maintenance treatment. The complainant also believed that the representative must have failed to explain to the speaker the great amount of care that was taken at this practice when doing this.

The speaker, and the four AstraZeneca representatives present, also failed to mention and acknowledge that AstraZeneca employed nurses to conduct an 'audit and step down' exercise in GP practices across the country. The complainant considered that this was a questionable activity, as even the speaker agreed that half-dose omeprazole (10mg) was less effective and he never used it. The complainant wondered if the speaker would disparage the nursing profession with the same vigour as he did pharmacists.

The complainant stated that during the presentation and the ensuing conversation the speaker made several references to pharmacists in a disparaging

context. He suggested that the complainant had not read the relevant research, he clearly doubted that the complainant would have been capable of doing such a thing. He also recounted how he had recently upset a young female hospital pharmacist.

At the end of the presentation an AstraZeneca representative suggested that pharmaceutical advisers were judged on their performance in terms of a 'cost per patient' measure. To the complainant's knowledge this was factually incorrect. The complainant believed that the inference of this comment was that the sole motivation for pharmaceutical advisers was to use cheap medicines regardless of efficacy. The complainant stated that this remark was in poor taste and wholeheartedly denied the inferences made. Indeed during the audit it was considered that a number of patients were more appropriately treated if left on omeprazole and others, who required life-long treatment doses of PPIs and had stopped taking them, were re-educated about the importance of continuing treatment.

The complainant alleged a breach of Clause 10.1 as the educational meeting clearly constituted 'disguised promotion'.

A breach of Clause 8.1 was alleged for deriding competitor's products. A breach of Clause 15 was also alleged.

Although the speaker was not, to the complainant's knowledge, an employee of AstraZeneca the complainant believed the company should be admonished for not ensuring that its invited guest speakers acted in a fair, responsible and professional manner. The presentation was against the spirit of the Code.

RESPONSE

AstraZeneca stated that the speaker's presentation was aimed to educate the GP audience about the nature of gastro-oesophageal reflux disease (GORD), the potential seriousness of the disease, the importance of clear diagnosis and use of a highly effective treatment. The 'roller-coaster' referred to by the complainant, and included as an illustration in the presentation, related to the dynamic state of reflux oesophagitis and that it was a relapsing remitting condition.

Whilst the speaker could not specifically recall his opening remarks in detail, he accepted that he made a comment during the middle of his presentation to the effect that, any group of highly educated healthcare professionals should not accept any guideline without critical appraisal. The style of the presentation was very much along the lines of a serious treatment of a serious topic and, whilst a degree of humour was injected into the presentation and discussion, this aspect was not intended to disparage or denigrate pharmacy as a profession.

Further to the allegation that the profession of pharmacy was disparaged, the speaker did not recall being specifically or intentionally so. Indeed, he could not recall the specific wording referred to by the complainant. During the course of his clinical practice he had regular interactions with ward pharmacists and pharmacy members of hospital drugs and therapeutics committees and held a high opinion of the pharmacy profession as a whole. Indeed, he regularly took advice from pharmacists within the clinical environment.

The intent of the speaker was to highlight the importance of GORD and effective treatment and present the relevant data in a way which reflected the overall balance of evidence. Data from trials positive for lansoprazole but which did not reflect the balance of evidence were not presented. In view of the large numbers of studies available in this area, and the limitations on time, the speaker acknowledged the fact that it was not possible to make reference to or present all the studies.

With regard to the allegations of 'scare mongering', the speaker assumed this related to quotations he used which were taken verbatim from the editorial by Cohen & Parkman (1999) and work by Lagergren (1999) both of which discussed the importance of full diagnosis and appropriate treatment of GORD.

AstraZeneca stated that the speaker was responsible for both the content and the production of his slides, which were his own personal property. The presentation was entitled 'Achieving Rational Disease Management in GORD', a highly suitable title for the GP presentation that was made on this occasion. AstraZeneca did not therefore accept the allegation that it influenced the content of the presentation or that it was specifically intended to undermine the work of GP advisers.

AstraZeneca gave details of the speaker's clinical and academic activities which showed that he was a well-respected authority on the use of PPIs and on no account could he be considered 'ill informed', as alleged by the complainant.

With regard to the specific allegations that the evidence presented by the speaker was misrepresented, AstraZeneca did not accept any breach of Clause 7.2.

Details of the topics covered and copies of the relevant slides were provided. Although the speaker had not kept a precise record as to which slides were used, AstraZeneca provided copies of those which, to the best of the speaker's recollection, were presented and related to the specific substance of the complaint.

The Medline research referred to was a personal search conducted by the speaker to find all published references to GORD therapies and, as this print-out was his own personal property and had been deleted, AstraZeneca was unable to provide a copy. The speaker did, however, pass a copy of the particular search to the complainant after the meeting. It was worthy of note that information found using a Medline search was provided in an abstract form only, ie it was a secondary source of information. It was generally considered inappropriate to base any conclusions on such without reference to the primary source.

- **Trials of comparative efficacy**

AstraZeneca stated that the comparative acid suppression efficacy data was taken from Geus (1997), which was used to demonstrate only the relative

efficacy of omeprazole 20mg od and lansoprazole 30mg (slide 12) which were the equivalent doses. Twice daily dosing was not discussed at this meeting due to its lack of relevance to general practice.

Comparative acid suppression efficacy data was also presented from Seensalu (1995) again highlighting the equivalent efficacy of omeprazole 20mg and lansoprazole 30mg in healthy volunteers (slide 13), and contrasted this with 20mg versus 15mg used in treatment. High dose data was not discussed, again, in view of the audience.

Comparative efficacy data was presented from Castell (1996). This study reflected the high efficacy of both lansoprazole 30mg and omeprazole 20mg. In this study, which was representative of maintenance treatment, lansoprazole 30mg and omeprazole 20mg were seen to be more effective than lansoprazole 15mg. Castell (1996) was selected due to the speaker's belief that appropriate maintenance in reflux oesophagitis was aggressive treatment of reflux disease using healing doses ie omeprazole 20mg and lansoprazole 30mg (slides 14-18). The speaker also specifically stated that, in his opinion, omeprazole 10mg was also insufficiently effective or optimal maintenance of reflux oesophagitis. This was in accordance with the summary of product characteristics for Losec, which stated that 20mg od was the recommended dose for maintenance.

- **Adverse drug reaction (ADR) rate data**

With regard to the comparison of adverse event rates presented (slide 20) AstraZeneca was assured by the speaker that he always prefaced this slide by stating that both lansoprazole and omeprazole were very well tolerated in normal practice. It was his usual practice to avoid making too much of this data and he usually stated that there seemed to be an advantage for omeprazole with respect to diarrhoea. He also always pointed out to his audience that this was not randomised controlled trial data and careful interpretation of the results was required.

Data from prospective trials was not presented; however, these trials were not ideal in the context of safety due to their size. These studies were not powered statistically to detect differences in adverse event rates between well tolerated medicines, the fact that they tended to only report drug reactions rather than adverse events biasing to the possibility of non-detection / non-reporting of true but unsuspected adverse drug reactions.

- **Effect of food on the bioavailability of lansoprazole**

AstraZeneca stated that the data presented (two studies demonstrating reduced bioavailability and one which showed no effect) which the speaker described in detail, was consistent (slide 19) with the lansoprazole licence which stated that 'To achieve the optimal acid inhibitory effect, and hence most rapid healing and symptom relief, Zoton 'once daily' should be administered in the morning before food' suggesting there was a clinical relevance. However, the speaker acknowledged at the meeting the current debate around the interaction of lansoprazole with food, notably that early work had shown differences but subsequent work had been inconsistent.

- **Price comparisons**

AstraZeneca stated that with regard to the relative costs of medicines, it was the belief of the speaker that the comments he made at the time were correct. He was happy to be corrected by the complainant after the talk.

- **Drug interactions**

The speaker had no recollections of discussing drug interactions. AstraZeneca would, however, point out that on the basis of a comparison from respective data sheets, lansoprazole had the potential to interact with oral contraceptives, food, sucralfate and antacids in contrast to omeprazole.

The speaker did not believe that he stated that any individual had not read relevant research and, indeed, the allegation that the pharmacist concerned would be unable to interpret the research was never implied. However, he recalled that on being questioned on a point of fact, he did correct the questioner stating that they were incorrect regarding that particular point.

In one-to-one conversations after the meeting, the speaker did recall saying that he had met a pharmacist who had not appreciated the severity of GORD and who had created guidelines without this appreciation, which had upset the individual involved. This was a statement of fact and no denigration of the profession of pharmacy as a whole was intended or implied.

AstraZeneca understood that, after all the GPs had left, one of its representatives during the course of a personal conversation sought clarification with the pharmacist as to the rationale for product switches. In particular, the importance of a reduction in cost per item prescribed versus an overall cost reduction. The company believed that this was a reasonable and valid point of discussion between a pharmaceutical industry representative and a healthcare professional.

As the speaker was presenting within his brief for the rational management of GORD, AstraZeneca considered that it was inappropriate that either he or the AstraZeneca representatives present should have mentioned or acknowledged the audit work carried out by its clinical nurses. This audit of the management of reflux was provided as a service to GPs. It was totally beyond the responsibility and remit for these nurses to make treatment recommendations on the basis of their audit work. At no time was this meant to infer that pharmaceutical advisers or indeed medical professionals would base prescribing decisions on cost decisions alone. On this basis, the company strongly denied that the remark was made in poor taste and disparaged pharmaceutical advisers and any breach of Clause 8.

With regard to the allegations of disguised promotion, the speaker had assured AstraZeneca that his aims had always been to promote the best-practice treatment, which he believed to exclude low dose PPI. Indeed, he spoke at this meeting against the use of both omeprazole 10mg and lansoprazole 15mg. In further illustration of the balanced approach adopted

by the speaker, AstraZeneca was aware that he was regularly invited to speak in an educational context with particular reference to the seriousness of GORD by other pharmaceutical companies. AstraZeneca, therefore, denied any breach of Clauses 10 and 15.

- **Full details of the meeting**

During a routine visit by an AstraZeneca representative, a doctor based at the medical centre expressed an interest in hearing a review of the most recent clinical evidence regarding the acid suppressant therapies. In recognition of his status as an opinion leader in the field of such disorders, it was agreed that the speaker in question would be suitable to present this information.

It was at the suggestion and agreement of the doctor that this educational meeting should take place at his practice. However, as he was unable to attend, another doctor, also from the medical centre, agreed to chair the meeting and was paid an honorarium. This being a subject of particular interest to GPs other GPs within the Primary Care Group were invited by the Chairman who also considered that the agenda was worthy of PGEA accreditation, which was duly applied for and granted.

A list of attendees was provided.

The meeting was held during the lunch hour; 30 minutes was allocated to the presentation with a further 10-15 minutes for a question and answer session. A copy of the programme was provided. AstraZeneca sponsored the lunch, with catering arranged by AstraZeneca.

- **Presentation**

AstraZeneca stated that the presentation covered the following points:

Introduction: the relapsing remitting nature of GORD in terms of the complaint of both symptoms and macroscopic oesophagitis.

The importance of GORD: The association of GORD symptoms with adenocarcinoma of the oesophagus and the need for effective diagnosis.

The effect of GORD on quality of life.

The relative efficacy of omeprazole 20mg, lansoprazole 30mg and lansoprazole 15mg. Acid suppression and clinical data.

Tolerability data and food interaction.

With regard to the slides dealing with the severity of GORD as a condition. These slides were taken from the journal Gut, which dealt with the effect of GORD on quality of life (slides 3 and 4) together with an editorial from the New England Journal of Medicine subsequent to the release of work showing an association of GORD and adenocarcinoma of the oesophagus (slides 5-11).

The speaker regularly used these slides to highlight the importance of GORD in terms of an impact on patients' lives (slides 3 and 14) and the importance of symptoms as a marker for future disease (slide 5). The epidemiology of GORD and adenocarcinoma of the oesophagus (slides 6-8), the inadequacies of current treatment (slide 9) a possible explanation of the aetiology of Barrett's oesophagus (slide 10) and the recommendation from the New England Journal of Medicine editorial on future treatment (slide 11).

The speaker concluded his talk with the recommendation that, based on his personal experience of seeing patients with the complication of reflux disease, the disease should not be trivialised and treatment should be maintained at appropriate doses, ie those used for treatment.

AstraZeneca stated that in accordance with accepted practice, there were no product exhibition stands or promotional materials available at the meeting. At no point during the meeting did any AstraZeneca representative ask questions or participate.

- **Details of the arrangements between AstraZeneca and the speaker**

AstraZeneca made the travel and accommodation arrangements for the speaker, who also received an honorarium. The invitation to the speaker was made by one of the local representative managers.

- **Was the speaker briefed by AstraZeneca?**

In a letter from AstraZeneca's Area Sales Manager, the speaker was briefed according to the following:

'The objective of the meeting is to review the clinical evidence for successful GORD management and to clearly highlight the consequences of inappropriate management of these patients. It is therefore important not only to highlight the consequences, but also to look at the solution of using the most effective therapy appropriately to give best patient care and cost effectiveness.'

The speaker was the only presenter at this meeting and no handouts were provided to delegates.

Three of the four AstraZeneca representatives present at the meeting had passed the ABPI representative's exam. The fourth was scheduled to take his examination for the first time in November and had until November 2000 to pass.

In summary, AstraZeneca therefore strongly denied that throughout the course of this meeting and presentation there was any breach of Clauses 7.2, 7.7, 8, 10 and 15.

In response to a request for further information, AstraZeneca stated that none of its personnel involved in organising the meeting had seen the speaker's slides prior to the meeting, and they were unaware of the specific content of the slides. In addition, no AstraZeneca personnel were involved in the provision of data or clinical papers to the speaker; he had provided these from a literature search that he personally carried out.

AstraZeneca confirmed that a second evening meeting was organised on the same day with, at the specific request of the organising GP, the same speaker being invited. The presentation was of a similar theme, with the speaker selecting the slides he considered appropriate for the meeting from his slide repertoire. No further meetings had been arranged where the speaker had been asked to present.

PANEL RULING

The Panel noted that AstraZeneca had approached the speaker and asked him to present at the meeting organised by AstraZeneca. The speaker was, as with any clinician, entitled to hold his own views and to express them. It would be inappropriate for companies inviting speakers to meetings to control the content of their presentations. To do so would detract from the value of industry sponsored meetings. However, it was not possible for a company to completely disassociate itself from the content of meetings which it sponsored especially where the meetings were initiated by the sponsoring company.

No judgement was being made in relation to the professional integrity of the speaker. One question to be answered was whether or not it was appropriate for AstraZeneca to have sponsored the meeting.

The Panel examined the slides supplied by AstraZeneca. The slides referred to GORD and the incidence of reflux oesophagitis / adenocarcinoma of the oesophagus. Reference was also made to the need to move the emphasis from symptom relief to healing regime investigation.

Slide 12 compared the acid suppression of lansoprazole 30mg once daily and 30mg twice daily with omeprazole 20mg once daily and 20mg twice daily. The data came from Geus *et al* (1997). The difference between omeprazole 20mg once daily and lansoprazole 30mg once daily was not statistically significant. These were the usual doses of the two medicines in GORD. The difference between the higher doses was statistically significant in favour of omeprazole although AstraZeneca stated that twice daily data was not discussed due to its lack of relevance to general practice. The Panel noted that the Geus data had been obtained from healthy volunteers although this was not mentioned on the slide.

Slide 13 referred to a 24 hour study by Seensalu (1995) of acid output in volunteers. As in the Geus study above, lansoprazole and omeprazole had been administered at their usual doses for GORD (30mg and 20mg od respectively) as well as at 60mg and 40mg daily respectively. Results for all of these doses were shown. There was no significant difference between omeprazole 20mg daily and lansoprazole 30mg daily. The difference between omeprazole 40mg daily and lansoprazole 60mg daily was again statistically significant in favour of omeprazole although, as above, AstraZeneca had stated that the high dose data was not discussed in view of the audience. The Seensalu study had also included lansoprazole 15mg although the results using this dose were not included on slide 13. The Panel noted that if all the data for lansoprazole had been included it would have been made clear that there was no statistical difference between omeprazole 20mg and lansoprazole 15mg or 30mg.

The Panel noted that the use of data from the Geus study and from the Seensalu study used in slides 12 and 13 had been ruled in breach of the Code in a previous case, Case AUTH / 677 / 2 / 98.

Slides 14, 15, 16 and 17 were each headed 'Lansoprazole 15mgs' and depicted the percentage healing rates adjusted for baseline oesophagitis, grades 2 or 3 and 4, after 8 weeks of omeprazole 20mg, lansoprazole 15mg or lansoprazole 30mg (Castell *et al* 1996). The Panel noted from the Zoton data sheet, however, that lansoprazole 15mg was not licensed as a healing dose in GORD; it was for maintenance therapy only. The slide summarising the Castell data stated that 'Omeprazole 20mg and lansoprazole 30mg were more effective than lansoprazole 15mg in oesophageal mucosa healing' and that 'Healing rates with omeprazole 20mg were significantly higher than with lansoprazole 15mg'. The Panel considered that these were unfair comparisons given that lansoprazole 15mg was not licensed to heal. The Panel noted that Castell *et al* had concluded that 'Compared with omeprazole 20mg, lansoprazole 30mg was as safe, was similarly effective with respect to oesophageal healing, and provided superior symptomatic relief, primarily early in treatment'. This point was not included in the slides.

Slide 19 posed the question 'Does food alter the availability' and offered the advice that lansoprazole should not be taken with food. The Zoton data sheet advised that to achieve the optimal acid inhibitory effect Zoton once daily should be administered in the morning before food. Zoton twice daily should be administered once in the morning before food and once in the evening. The Panel did not consider that slide 19 was unreasonable given the content of the data sheet.

Slide 20 dealt with the Prescription Event Monitoring data (PEM) and referred to the incidence of most commonly reported events. The Panel noted that none of the data from the clinical trials were given. The PEM data merely reflected the reporting of the events. The Panel noted that although the slide showed that the incidence of diarrhoea and headache with omeprazole was less than half of that experienced with lansoprazole, the slide did not reflect the Losec data sheet which stated that the reactions might be severe enough in a small number of patients to require withdrawal of therapy. The slide did not refer to the similar profiles of the two medicines.

The Panel noted that the speaker acknowledged he had made a misleading cost comparison by stating that high dose generic ranitidine was significantly cheaper than half dose PPI. The Panel noted that 28 days' supply of 300mg bd of ranitidine was listed in the September Drug Tariff as costing £38.56 with Zoton 28 x 15mg costing £14.21 (ref MIMS September 1999).

The Panel considered that although the speaker was an independent physician he had been briefed by AstraZeneca and the company had facilitated his attendance at the meeting. It was therefore not possible for AstraZeneca to totally dissociate itself from what he had said. If AstraZeneca were not responsible then the effect would be for companies to use independent experts as a means of avoiding the requirements of the Code.

Overall the Panel decided that the comparisons presented regarding efficacy, side-effects and costs were

misleading and unfair for the reasons noted above. It had not been made clear that some of the comparative efficacy data were from healthy volunteers (Geus *et al* 1997). The Panel ruled a breach of Clause 7.2 of the Code. A breach of Clause 8.1 was also ruled as the material disparaged Zoton. No breach of Clause 7.2 of the Code was ruled with regard to data presented about an interaction between Zoton and food.

With regard to the allegations that the speaker was disparaging of pharmacists, the Panel noted that the parties' accounts differed. There was no way of knowing precisely what had been said and the Panel therefore ruled no breach of Clause 8.2 the Code.

With regard to the allegation that the meeting constituted disguised promotion, the Panel was concerned that the letter of invitation was headed 'Clinical Meeting Invitation'. Some way down the letter it was stated that following the meeting there would be a lunch sponsored by Astra Pharmaceuticals. It appeared that the meeting and the lunch were independent of each other. The whole meeting had in fact been sponsored by AstraZeneca but this had not been made clear. Four AstraZeneca representatives had attended the meeting; there had been eleven delegates and the chairman. The Panel noted that the presentation had been unfair and misleading. The Panel considered that the meeting was in effect a promotional activity which had been publicised as an educational meeting. The Panel ruled a breach of Clause 10.1 of the Code as alleged.

The Panel queried whether the honorarium paid by the company to the Chairman was reasonable given that the meeting was scheduled to last for 45 minutes (30 minute presentation followed by 15 minutes of questions).

The Panel noted that the complainant had alleged a breach of Clause 15 of the Code for presenting research in a biased manner. The Panel considered that this allegation was covered by its ruling of a breach of Clause 7.2.

APPEAL BY ASTRAZENECA

AstraZeneca said that given the length of the complaint and ruling, it had addressed the points raised in turn.

1 AstraZeneca acknowledged and totally agreed with the Panel's expressed statement that 'It would be inappropriate for companies inviting speakers to meetings to control the content of their presentations' and accepted that 'it was not possible for a company to completely dissociate itself from the content of meetings which it sponsored especially where the meetings were initiated [AstraZeneca's emphasis] by the sponsoring company.'

On this occasion the proposal for the meeting in question was initiated by the GP based at the medical centre. Moreover, it was at the suggestion and with the agreement of this GP that this educational meeting should take place at his practice and that the speaker involved would be the most suitable to present the most recent clinical evidence regarding acid suppressant therapies.

AstraZeneca reiterated, as in its initial response, that it had had no involvement in either the content of the speaker's talk or the slides he selected for use from his own personal slide repertoire appropriate for the particular occasion in question. Indeed, the speaker was a regular Internet user and used it to source all his data. Thus, AstraZeneca did not accept the inference that AstraZeneca influenced the content of the presentation, as stated in the Panel's ruling.

The fundamental principle in the case was how to determine compliance with the Code for presentations prepared by independent speakers which had not been pre-vetted by a company, in recognition of the importance of preserving the speaker's independence. AstraZeneca accepted that it was the company's responsibility to ensure compliance with the Code for company sponsored meetings. However, AstraZeneca advocated a pragmatic approach so that the content of a slide and accompanying verbal comments from a speaker were taken as whole rather than assessing the slide content alone. This was in contrast to promotional materials, such as detail aids, for which a company was wholly responsible. This principle was important as pre-vetting of slides was not considered acceptable by many speakers. If assessment of compliance with the Code was not made pragmatically this would result in independent speakers refusing to participate in company sponsored meetings to the detriment of postgraduate education.

Regarding the presentation, AstraZeneca was advised by the speaker that, on this occasion, his intent was to highlight the importance of GORD and effective treatment, rather than the need to shift the emphasis from symptom relief to healing regimen investigation, as incorrectly stated in the Panel ruling.

The Panel ruled the following slides to be misleading and in breach of Clause 7.2:

Slide 12 – this slide was criticised by the Panel for not making reference to the fact that the comparative data presented related to healthy volunteers, Geus *et al* (1997). As stated previously, AstraZeneca did not consider it appropriate to interfere with the slides of an independent clinical expert and it did not have the opportunity to review these slides. Although the slide omitted to include the reference to volunteers or provide a key to the use of the asterisk, ie the level of significance, the speaker had advised that, as far as it was his recollection, verbal reference would have been made to both points.

Slide 13 – this slide referred to data by Seensalu (1995). Again, the speaker selected this sub-set of data to present on this slide on the basis of his clinical opinion and experience. He had assured AstraZeneca that the point of presenting this data was to highlight the equivalent efficacies of omeprazole 20mg and lansoprazole 30mg in healthy volunteers. This was verbally put into context with regard to both omeprazole 20mg and 15mg lansoprazole, the doses that were regularly used in clinical practice.

The Panel noted that the use of data from Geus and Seensalu, in slides 12 and 13, respectively, had been ruled in breach on a previous occasion. Whilst the speaker would have been unaware of the technicalities, these breaches were ruled on the

presentation of the data, rather than the use of the data *per se*, namely Clause 7.6 (graphical misrepresentation) and Clause 7.2 (not clearly indicating that the data was from healthy volunteers), respectively. However, it was pertinent to note that the data was presented in slide 12 in tabular form, not as a bar chart, and that in slide 13 reference to 'volunteers' was included in the title.

Slides 14, 15, 16 and 17 – whilst no mention of 15mg lansoprazole was included in slide 13, reference to lansoprazole 15mg was then included in slides 14 to 17. The speaker had assured AstraZeneca that he was fully aware of the fact that lansoprazole 15mg was not licensed for healing and would have reminded the audience of such. Work by Castell (1996) was selected by the speaker as, in his opinion, it was representative of maintenance treatment, and was consistent with his belief that appropriate maintenance in reflux oesophagitis was aggressive treatment of reflux disease using healing doses.

As a general principle, acid suppression data were used only as a marker of clinical efficacy. The presence of a clinically relevant difference in acid suppression between omeprazole 20mg and lansoprazole 15mg was supported by two clinical comparisons of these doses. In GORD healing (Castell, 1999) and maintenance (Baldi, 1996) omeprazole 20mg had been shown to be significantly more effective than lansoprazole 15mg. These trials, as the only randomised controlled clinical studies comparing these doses, formed the balance of evidence in reflux disease. Finally, as there was health authority pressure advocating the use of lansoprazole 15mg for healing, even though this was not a licensed dose, the speaker considered it appropriate and not unfair to include reference to this dose, as it addressed a legitimate concern of the medical profession.

The point raised by the Panel concerning the omission of one of the conclusions of Castell, namely that 'compared to omeprazole 20mg, lansoprazole 30mg was safe, was similarly effective with respect to oesophageal healing and provided superior symptomatic relief' was, again, reflective of the speaker's selection of data for inclusion in his slide. However, in addition to the conclusion made on slide 18, the point was addressed verbally.

Slide 20 – the speaker had assured AstraZeneca that he always prefaced this slide by stating that both drugs were equally well tolerated in clinical practice. The speaker considered it useful to present Prescription Event Monitoring data as these were supplementary to data from randomised, controlled, clinical trials and the speaker's clinical experience. However, as the data was not based on such trials, the speaker had assured AstraZeneca that he avoided making too much of the data and advocated careful interpretation of such. As the slide was not designed to be a comparison of the respective data sheets for omeprazole and lansoprazole, it would be inappropriate to draw attention to any dissimilarity stated therein.

2 AstraZeneca did not accept the allegation that the speaker was fully briefed by AstraZeneca. Indeed, the speaker was anxious to reinforce his independent status and categorically denied the suggestion that he was a promotional agent of AstraZeneca. Indeed, he regularly made similarly comments at meetings held on behalf of other pharmaceutical companies.

On the basis of the above, notably that the speaker presented his own opinions, selected data and clinical experience, AstraZeneca did not consider that the presentation, both the slides and the accompanying oratory, was either misleading or unfair.

AstraZeneca therefore appealed against the Panel's ruling of a breach of Clause 7.2.

Similarly, the speaker and AstraZeneca did not accept that there was any disparagement, implied or otherwise, of Zoton. Based on the speaker's opinion and clinical experience, the presentation was a factual comparison of the two drugs.

AstraZeneca therefore appealed against the Panel's ruling of a breach of Clause 8.1.

AstraZeneca noted the Panel's expressed concern for the honorarium paid to the Chairman and explained that in addition to chairing the meeting, the Chairman was responsible for organizing the PGEA accreditation and the circulation of the meeting invitation. Thus, AstraZeneca considered the amount paid to be reasonable.

APPEAL BY COMPLAINANT

The complainant said that she was appealing with respect to the Panel's ruling of no breach of Clause 8.2.

It would be recalled that her account of the speaker's remarks (disparaging pharmacists) differed from that of the speaker himself, who denied making such remarks. The Panel decided that there was no way of knowing precisely what had been said, it was really a case of 'His word against mine'.

That being the case, the complainant submitted in support of her appeal statements from three general practitioners present who recalled the remarks / sentiments expressed.

RESPONSE FROM ASTRAZENECA

AstraZeneca said that it had acknowledged responsibility in having sponsored this educational meeting and accepted that this included the expressed general views and opinions of the invited speaker which the company was aware of beforehand. However, AstraZeneca confirmed that it was not aware of the speaker having previously expounded any negative opinion of the profession of pharmacy.

On this basis, if a chance remark made in jest caused any offence to a particular member of the audience and it was not possible for this to be foreseen by the sponsoring company, AstraZeneca did not consider it reasonable for the company to be held responsible under the Code. Furthermore, it was pertinent to note that it was at the invitation of the local AstraZeneca representative that the complainant was invited. Similarly, it was not deemed necessary or appropriate to advise the speaker that there was a member of the pharmacy profession, namely the complainant, present in the audience as no issues were expected.

In illustration of the speaker's high opinion of pharmacy, he had advised AstraZeneca that during the course of his clinical practice he had regular interactions with pharmacists, for example on the wards and with those who were members of hospital drugs and therapeutics committees. He had previously spoken at educational events for pharmacists. Moreover, he regularly took advice from pharmacists within the clinical environment.

In reflection of his expertise and professional standing, the speaker was regularly invited to present on his speciality to a wide range of audiences, not necessarily industry sponsored meetings. Consequently, he was unable to specifically recall the detail of his opening remarks made at this particular meeting and was therefore unable to refute the allegation. AstraZeneca was assured by the speaker that, if indeed such a comment was made, it was never his intent that it should infer or imply disparagement to either the complainant or the profession of pharmacy as a whole. The speaker did recall, however, making a comment during the middle of the presentation to the effect that any group of highly educated healthcare professionals should not accept any guideline without critical appraisal. This criticism was primarily aimed at doctors who did not engage in the process of developing guidelines, but passively accepted such protocols developed by other healthcare professionals.

The speaker had confirmed that, during his presentation, the style adopted was intended to be a serious treatment of a serious topic and, whilst a degree of humour was injected into the discussion, this aspect was not intended to disparage or denigrate pharmacy as a profession.

The speaker did not believe that he stated that any individual had not read relevant research. Indeed, he had assured AstraZeneca that the allegation that the complainant pharmacist would be unable to interpret research was neither in his mind or implied. However, he did recall correcting, when questioned on a point of fact, that the questioner was wrong.

On the basis of the above, if the alleged remark was made AstraZeneca did not believe that it was the speaker's intent to disparage the complainant, either as an individual or the profession of pharmacy as a whole. One of the letters submitted by the complainant stated 'This was done in jest'. However, such matters were often of a personal opinion and, although three attendees had supported the complainant's contention, AstraZeneca drew attention to the fact that these represented, having excluded the AstraZeneca representatives, a minority of the attendees.

In view of the circumstances of this particular complaint, AstraZeneca requested guidance from the Appeal Board as to whether it fell under the remit of the Code.

FURTHER COMMENTS FROM THE COMPLAINANT

In response to the comment that it was at the invitation of the local AstraZeneca representative that she was present at the meeting (thereby suggesting that any denigration of pharmacists had not been anticipated) the complainant said that this was not the case. The complainant was not personally invited to the meeting and, as far as she knew, the AstraZeneca representative could not have predicted with any certainty her presence at a meeting that was, after all, targeted at GPs. The complainant also found it rather incongruous that, at an educational meeting supposedly about the relapsing/remitting nature of oesophageal reflux disease, the guest speaker should take such an early opportunity to denigrate, very specifically, the pharmacy profession. This led the complainant to believe that the speaker had been given information prior to the meeting about the practice and her activities within it.

With respect to AstraZeneca's reference to one of the submitted letters of support, it made reference to one particular quote 'This was done in jest' as an illustration of the 'degree of humour' (AstraZeneca's words not the complainant's) supposedly injected into the proceedings. The complainant drew attention to the rest of the relevant sentence 'but *(this was)* clearly a put down' and the contents of the other two letters submitted which, she was sure would be agreed, did not suggest that was any element of 'jest' in the comment at all.

With respect to AstraZeneca's comments that the three attendees who submitted statements made up the minority of the audience, the complainant's response was:

- She was only given a very short space of time to formulate her appeal. In this time she was able to contact five of the GPs present, all of whom verbally testified to the 'incident' but only three of whom were able to produce a letter of support in time for the given deadline. General practitioners (and prescribing advisers) were very busy people and clearly, due to pressure of work, did not have the available time and resources that the medical and regulatory affairs department of a multinational pharmaceutical company had at its disposal. With a larger time frame the complainant was confident that more responses could have been gathered.

- The complainant considered that it was quite possible to draw a picture of the events and some idea of the audience's reactions from the three statements already gathered. Surely AstraZeneca could not possibly be suggesting that these statements were in any way invalid or less meaningful because there were only three of them? To suggest this was to imply that these general practitioners were lying about the events of that day. The complainant would implore AstraZeneca to take statements from its representatives.

APPEAL BOARD RULING

The Appeal Board noted that the degree to which pharmaceutical companies were involved with educational meetings would differ. At one extreme a meeting could be sponsored through an independent third party whereby a company did no more than provide funds to cover expenses. In such circumstances it was difficult to see that a company

could be held responsible for what speakers said at the meeting. At the other extreme a company could initiate a meeting, choose the speakers and brief them as to what they should say, provide slides for the speakers and choose and invite the delegates. In such circumstances the Appeal Board considered that a company would be responsible for what speakers said. The whole proceedings of the meeting would be subject to the Code. If this were not the case then a company could employ independent experts to say what it, as a company, could not say, and so avoid the restrictions of the Code. Companies would normally be aware in advance of the general views of speakers they invited to present at meetings. In determining whether a pharmaceutical company was responsible for what was said at a meeting, particularly when its involvement was neither at one extreme or the other, then the whole of the arrangements would have to be considered including, *inter alia*, who initiated the meeting and chose the subject, who chose and invited the speakers, whether the speakers were briefed by the company and who chose and invited the delegates. Each case would have to be considered on its own merits.

The Appeal Board fully appreciated the difficulties for companies asking independent speakers to present at such meetings. It would be unsatisfactory for companies to dictate to speakers what they should present. On the other hand, depending on the degree of involvement, companies might have to ensure compliance with the Code. It could clearly be difficult to achieve the right balance in these regards. No judgement would be made as to the professional integrity of a speaker. It was not a question of what the speaker presented it was a question of whether it was appropriate for the company to have sponsored the presentation.

In the case now before it the Appeal Board noted that, during a routine visit from a local representative, one of the doctors at the medical centre had expressed an interest in hearing a review of the clinical evidence regarding acid suppression data. It was agreed that the speaker in question should be invited. The subsequent invitation to the meeting stated that the speaker's presentation was entitled 'Achieving rational disease management in GORD'. The invitation gave further details and stated that 'The meeting will focus on issues which need to be addressed when aiming to rationalise prescribing for GORD. When trying to achieve appropriate management of any disease there is always a dilemma of how to balance patient expectation and prescribing costs. [The speaker] explores the consequences of sacrificing either one in preference to the other'. In the Appeal Board's view the meeting did not appear to be the clinical review as first requested.

The Appeal Board noted that the doctors at the medical centre at which the meeting was held had, until recently, been high users of Losec, but in collaboration with the complainant they had reviewed their PPI prescribing and decided that, where appropriate, patients should be given a maintenance dose of Zoton. The speaker's opinion was that appropriate maintenance in reflux oesophagitis was aggressive treatment using healing doses. The Appeal Board noted the company representatives' submission that the speaker had spoken for AstraZeneca on a number of occasions in the past. The company was likely to be aware of his opinions with regard to the use of PPIs. AstraZeneca had facilitated the speaker's attendance at the meeting; the company had briefed him as follows: 'The objective of the meeting is to review the clinical evidence for successful GORD management and to clearly highlight the consequences of inappropriate management of these patients. It is therefore important not only to highlight the consequences, but also look at the solution of using the most effective therapy appropriately to give best patient care and cost effectiveness'.

Overall the Appeal Board considered that given AstraZeneca's involvement with the meeting, it was responsible for what the speaker said. The speaker's attendance at the meeting had been facilitated by the company and he had been briefed as to the objective of the meeting. The Appeal Board considered that the meeting was promotional. The Appeal Board noted that no judgement was being made in relation to the professional integrity of the speaker. The Appeal Board noted AstraZeneca's submission that a pragmatic approach should be taken so that the content of the slide and accompanying verbal comments from the speaker were taken as a whole rather than assessing the slide content alone. There was of course no way of knowing what the speaker had said. The Appeal Board considered that the comparisons of Zoton and Losec in the slides, irrespective of any verbal comment, were misleading and unfair as alleged. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2 and 8.1.

The appeal on this point was thus unsuccessful.

With regard to the complainant's appeal concerning the allegation that the speaker disparaged pharmacists, the Appeal Board noted the differences between the parties' accounts; it was thus impossible to tell where the truth lay. The Appeal Board considered, however, that should disparagement have occurred then AstraZeneca could not be held responsible for it. In this case AstraZeneca would have known the speaker's views with regard to the use of PPIs but it had no reason to believe that he would disparage certain members of the audience – if indeed he did. Companies could not be held responsible for chance remarks made by speakers at meetings they had sponsored. The Panel's ruling of no breach of Clause 8.2 was upheld.

The appeal on this point was thus unsuccessful.

Complaint received **23 September 1999**

Case completed **16 March 2000**

CASE AUTH/936/9/99

GENERAL PRACTITIONER v ROCHE CONSUMER HEALTH

Rennie Duo 'Dear Doctor' letter

A general practitioner complained about a Rennie Duo 'Dear Doctor' letter produced by Roche Consumer Health. A table compared the active ingredients of Rennie Duo with those of the most frequently prescribed alternative proprietary alginate. 10ml of Rennie Duo and 10ml of the comparator were shown to have 300 and 500 (no units stated) of sodium alginate respectively. The complainant stated that the 'Dear Doctor' letter claimed that Rennie Duo contained less sodium than a standard proprietary alginate. The complainant understood that both Algicon and Topal contained either no or very low amounts of sodium. The complainant also stated that with regard to the table of active ingredients, the quantity of each should have been quoted in mmols.

The Panel noted that the letter referred to prescribing Rennie Duo (a GSL restricted to pharmacy product) and therefore came within the scope of the Code.

The Panel noted that the table clearly compared the active ingredients (including sodium alginate) per 10ml dose of Rennie Duo with those of the most frequently prescribed standard proprietary alginate. The comparison was therefore of two liquid compound alginate preparations. In that regard the Panel noted that Topal was a solid dose formulation. With regard to Algicon, its active ingredients were different to those listed in the table. The Panel considered that as the comparator was clearly stated, and its active ingredients listed, there was no express or implied comparison with Topal or Algicon as inferred by the complainant. No breach of the Code was ruled in that regard.

The Panel noted that the figures featured in the table referred to the number of mg of each ingredient. The Panel considered that whilst it would have been useful to include the units the failure to do so was not misleading. No breach of the Code was ruled.

On appeal by the complainant, the Appeal Board noted that the letter stated that Rennie Duo was significantly different to the most frequently prescribed alternative. This was followed by the table of active ingredients which, in terms of sodium-containing compounds, showed that Rennie Duo contained sodium alginate (300) and no sodium bicarbonate. The comparator contained sodium alginate (500) and sodium bicarbonate (267). The Appeal Board considered that the table invited readers to add up the figures and assume that Rennie Duo contained significantly less sodium than the standard proprietary alginate. The Appeal Board noted that the table only listed active ingredients and so while no sodium bicarbonate was declared for Rennie Duo it was included as an excipient and would contribute to the total sodium content of the product.

The Appeal Board noted that halfway through the letter, beneath the table and in the same font size, it was stated that '… Rennie Duo also gives you other significant benefits:' the first of which was '… calcium and magnesium based antacids with little available sodium, making it a suitable treatment for heartburn and acid indigestion throughout pregnancy'.

The Appeal Board considered that, together, the quantitative data in the table and the statement about significant benefits implied that the sodium content of Rennie Duo was an important issue with clinical benefits. The Appeal Board considered that overall the letter implied that Rennie Duo contained significantly less sodium than its competitors which was misleading. A breach of the Code was ruled.

A general practitioner submitted a complaint about a 'Dear Doctor' letter produced by Roche Consumer Health (ref L01798/8.99). The letter introduced Rennie Duo as the new dual-action approach for rapid effective relief of dyspepsia and reflux. A table compared the active ingredients of Rennie Duo with those of the most frequently prescribed alternative standard proprietary alginate. 10ml of Rennie Duo and 10ml of the comparator were shown to have 300 and 500 (no units stated) of sodium alginate respectively. The letter also stated that Rennie Duo contained calcium and magnesium based antacids with little available sodium.

COMPLAINT

The complainant stated that the 'Dear Doctor' letter claimed that Rennie Duo contained less sodium than 'a standard proprietary alginate'. To the complainant's understanding of the British National Formulary both Algicon and Topal contained either no or very low amounts of sodium.

The complainant also noted that in the table no numerator was given for the amounts of various chemicals – one had to assume it was mg, but different salts had different ionic valency compositions and consequently these results should be quoted in mmols.

RESPONSE

Roche Consumer Health stated that it had never made any comparative claim that Rennie Duo contained less sodium than any other product. Such a claim did not appear in the 'Dear Doctor' letter and the company had not used it any other promotional material.

The only comparison that was made in the 'Dear Doctor' letter was the comparison of active ingredients which appeared in the table. This table was included to show that Rennie Duo contained both antacids and a rafting agent. Sodium was only mentioned in the 'Dear Doctor' letter in the statement 'Roche Rennie Duo contains calcium and magnesium based antacids with little available sodium…' and did not appear until the third paragraph after the table. As neither the table nor the main text made any comparison of sodium content between Rennie Duo and any other product, it would be irrelevant to use mmols.

Roche Consumer Health confirmed that the figures in the table did indeed refer to the number of mg of each ingredient. For the sake of clarity, it might have been better to have included the units and they would be included if the table was used again in any future promotional material; however, the company submitted that the units would have been clear to the vast majority of readers and, consequently, would not have caused any confusion.

It was worth noting that the units in mg were included in the product information which appeared on the back of the 'Dear Doctor' letter.

PANEL RULING

The Panel noted that the letter referred to prescribing Rennie Duo (a GSL restricted to pharmacy product) and therefore came within the scope of the Code.

The Panel noted that the table clearly compared the active ingredients (including sodium alginate) per 10ml dose of Rennie Duo with those of the most frequently prescribed standard proprietary alginate. The comparison was therefore of two liquid compound alginate preparations. In that regard the Panel noted that Topal was a solid dose formulation. With regard to Algicon, its active ingredients were different to those listed in the table. The Panel considered that as the comparator was clearly stated, and its active ingredients listed, there was no express or implied comparison with Topal or Algicon as inferred by the complainant. No breach of Clause 7.2 was ruled.

The Panel noted that the figures featured in the table referred to the number of mg of each ingredient. The Panel considered that whilst it would have been useful to include the units the failure to do so was not misleading. No breach of Clause 7.2 was ruled.

APPEAL BY COMPLAINANT

The complainant stated that Rennie Duo had been advertised as being better than the leading selling product because it contained less of certain ingredients, namely sodium. Sodium was implicated in hypertension and therefore the company was hoping to persuade doctors that its product could be used for people who were at risk of hypertension. This would appear to be a direct analogy to a case where a company advertised its product against an individual alternative product purely on the basis of price. The complainant was aware that there were sections of the regulations which prohibited the use of a price comparison against an individual product in the same category. He stood to be corrected if he was wrong. The complainant was under the impression that where a price comparison was made, the comparison had to be made against all products in the same category. Therefore the complainant felt that if any individual component of a medicine was compared favourably against one product, it should be made clear in the advertisement or mailing that there were other products that also offered the same advantage.

RESPONSE FROM ROCHE CONSUMER HEALTH

Roche Consumer Health stated that no comparative claim that Rennie Duo contained less sodium than any other product had been made in any of its promotional material. It had never stated that Rennie Duo was 'better' than any other product.

Roche Consumer Health never made any claim that the product was suitable for use in hypertension and it did not think that anyone reading the 'Dear Doctor' letter would be left with that impression.

The only comparison made was of the active ingredients against the leading liquid alginate to show that Rennie Duo contained both antacids and a rafting agent. Since Roche Consumer Health had not made any of the claims alleged by the complainant, it remained its belief that there had been no breach of Clause 7.2.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant stated that if the amount of sodium was stated as being less than the market leader, then it should also be compared with all other similar products, some of which had the same amount of sodium or less than Rennie Duo. The complainant conceded that no specific comment was made about hypertension in the advertisement. However, he thought that many doctors would read into an advertisement which contained sodium content an indication that patients who would be aggravated by high sodium intake would be adversely affected by the market leader and therefore patients with hypertension could be better off using Rennie Duo than the market leader.

The complainant stated that everyone was aware that something did not have to be boldly stated for hints to be made and taken, and much of the best advertising both in print and in other media was made by the use of suggestion and inference, giving the reader the bonus of feeling ownership of the deduction that he or she had made and therefore reinforcing the message received.

APPEAL BOARD RULING

The Appeal Board noted Roche Consumer Health's submission that the purpose of the 'Dear Doctor' letter was to introduce the reader to the dual action of Rennie Duo ie that it contained both an antacid component and a rafting agent. The comparison was clearly between Rennie Duo and the most frequently prescribed alternative. There was no express or implied comparison with Topal or Algicon. The letter stated that Rennie Duo was significantly different to the most frequently prescribed alternative. This was followed by the table comparing the active ingredients of Rennie Duo with those of the standard proprietary alginate which gave the quantities of each ingredient. In terms of sodium-containing compounds Rennie Duo contained sodium alginate (300, no units stated) and no sodium bicarbonate. The comparator contained sodium alginate (500) and sodium bicarbonate (267). The Appeal Board considered that the table invited readers to add up the figures and assume that Rennie Duo contained significantly less sodium than the standard proprietary alginate. The Appeal Board noted that

the table only listed active ingredients and so while no sodium bicarbonate was declared for Rennie Duo it was included as an excipient and would contribute to the total sodium content of the product.

The Appeal Board noted that halfway through the letter, beneath the table of data and in the same font size, it was stated that '… Rennie Duo also gives you other significant benefits:' the first of which was '… calcium and magnesium based antacids with little available sodium, making it a suitable treatment for heartburn and acid indigestion throughout pregnancy'. The Appeal Board considered that, together, the quantitative data in the table and the statement about significant benefits implied that the sodium content of Rennie Duo was an important issue with clinical benefits. The Appeal Board considered that overall the letter implied that Rennie Duo contained significantly less sodium than its competitors which was misleading. A breach of Clause 7.2 was ruled.

The appeal was thus successful.

Complaint received **30 September 1999**

Case completed **18 February 2000**

CASE AUTH/938/10/99

THE NATIONAL PHARMACEUTICAL ASSOCIATION v TRINITY

Sales methods

The National Pharmaceutical Association complained about a booklet produced by Trinity in support of its modified release (MR) preparations. The booklet explained that as MR preparations were not included in the Drug Tariff any brand could be dispensed against a generically written prescription with the full cost of that brand being attributed to a GP's prescribing costs regardless of any discount to the pharmacist. An expensive medicine for the GP might be financially more attractive to the pharmacist if a large discount were negotiated. It was alleged that the statements 'There is no legal obligation for a pharmacist to dispense the least expensive version of any drug' and 'Any discount received by a pharmacist is not transferred to a GP's prescribing costs. In other words, additional profit for the pharmacist could mean additional cost to the surgery', were misleading and disparaging to pharmacists.

The Panel noted that discounting was a long established business practice but that when pharmacists were reimbursed the overall benefit of negotiating discounts was reduced by a system of claw back. The Panel considered that the statement 'In other words, additional profit for the pharmacist could mean additional cost to the surgery' did not represent the whole picture. No mention had been made of the claw back. The booklet was too simplistic and in the Panel's view gave the impression that pharmacists could benefit directly from additional cost to the surgery. The Panel considered that the booklet was misleading in this regard and a breach was ruled. It was also ruled in breach as it was disparaging to pharmacists.

On appeal by Trinity against the ruling that the claim was misleading, the Appeal Board considered that the statement at issue was factual, accurate and not misleading. No breach of the Code was ruled in this regard.

The National Pharmaceutical Association (NPA) complained about a booklet produced by Trinity Pharmaceuticals Ltd in support of its modified release (MR) preparations. The booklet explained that as MR products were not included in the Drug Tariff a doctor would not know what a generically written prescription would cost. A pharmacist was free to dispense any brand of the MR product and the full NHS cost of that brand would be attributed to the GP's prescribing costs regardless of any discounts available to the pharmacist. The pharmacist was not bound to dispense the cheapest generic preparation and a more expensive medicine might be financially more attractive if a large discount were negotiated. Page 4 of the booklet, headed 'Doesn't the chemist have to dispense the cheapest?' stated that 'In other words, additional profit for the pharmacist could mean additional cost to the surgery' and the following page stated 'Any discounts obtained by the pharmacist are not passed on to the surgery'.

COMPLAINT

The NPA said that its Board of Management had asked that the Authority be contacted about the marketing activities of Trinity Pharmaceuticals. Correspondence was provided to explain the background.

A letter sent by the NPA to Trinity on 22 July stated:

'I have seen a copy of promotional material you appear to be using to persuade prescribers to specify your brands of modified release products. The NPA represents the interests of almost all the owners of community pharmacies in the UK and this matter has been brought to my attention by members.

It strikes me that your message to prescribers is simple – Trinity's products are less expensive, by prescribing them by name you not only reduce your prescription costs but you also ensure continuity and thus confidence for the patient.

I would not argue with the thrust of your campaign but I must point out that your remarks under the

heading 'Doesn't the chemist have to dispense the cheapest?' (and on the following page) might be taken to indicate that pharmacists are benefiting from discounts at the expense of doctors' prescribing costs. As you know, the NHS claws back pharmacists' discounts and does so regardless of whether a major brand, a Trinity product or a generic is dispensed. Your remarks are misleading, they do nothing to further your legitimate sales pitch but are potentially harmful to prescribers' perception of their local pharmacists.

Perhaps you would be kind enough to reconsider the content of your promotional material.'

Trinity's reply dated 27 July stated:

'In response to your letter to …….dated 22 July regarding our promotional material. I am very pleased that you agree with the thrust of our campaign which is being increasingly welcomed by many health authorities and PCGs [primary care groups] as a means of saving on prescribing costs and simultaneously ensuring continuity of patient medication.

I am concerned that you feel that our material is misleading. As far as I am aware the document is factually correct and whilst your argument regarding clawback has some merit on a global level I am sure that you will accept the legitimate right of GPs, PCGs and health authorities to manage their own local costs to the best advantage of their patients.

Notwithstanding the above I have taken on board your concerns and will ensure that the message which we deliver is not detrimental to the relationship between the various health care professionals who form our growing customer base.'

A further letter from the NPA to Trinity dated 10 August stated:

'Thank you for your letter dated 27 July. I am grateful that you are determined not to undermine relationships between healthcare professionals. My original concern stemmed from a document I received from a health authority pharmaceutical advisor. Knowing the professional stance such people take, it seemed important to ensure that you had the opportunity to correct any misapprehensions.

I infer from your letter that, whereas you may be intending to change the way you handle your messages, you do not intend to change the documentation. I am disappointed at this and hope you might reconsider.'

The NPA stated that at its September meeting, Board members had reported that two health authorities had written to their general practitioners and pharmacists commenting unfavourably on Trinity's activities. Two Board members had also said that Trinity staff offered to 'Save you time doctor' by accessing the prescriber's computer system and amending the drug database.

The NPA was particularly concerned that the company's published information could be taken to imply that pharmacists were profiteering at the expense of general practitioners. As would be appreciated, the NHS reported to GPs with their prescribing costs and these were based on manufacturer list prices for brands and Drug Tariff prices for products prescribed generically. There was no direct link between the price paid for prescription medicines by pharmacists and a GP's prescribing costs.

The NPA did not believe that the response it received on July 27 from Trinity was adequate and it certainly appeared that there was disquiet about its activities amongst health authorities.

RESPONSE

Trinity stated that it had not seen any of the health authority correspondence referred to by the NPA and nor had it been advised of the 'two Board members' who alleged that Trinity staff had been offering to access the GP's computer system. Trinity was thus unable to comment upon these points unless the NPA was able to provide further information in order that Trinity could make the necessary enquiries.

The NPA appeared to be mostly concerned with the sentiments expressed in page 5 of Trinity's promotional material. The contents of this material were factually accurate as it related to MR brands. GPs who prescribed MR products generically did leave themselves in the hands of the pharmacists to select which was dispensed. Since many generic MR products had a relatively high list price and, often, a heavily discounted supply price the choice of product would inevitably be influenced by the available margin. This was in Trinity's view legitimate and fair business practice for the pharmacist – they had a business to run and were encouraged by the reimbursement system to negotiate for the best supply price. However, the NPA was incorrect in stating that 'There is no direct link between the price paid for prescription medicines by pharmacists and a GP's prescribing costs'. The best 'deal' from a generic supplier for an MR product might well be on the product with the highest list price. Trinity's business proposition was based around the fact that only by writing by brand name for MR products did the GP have control over not only the cost of his prescribing but also patient continuity. This had been widely accepted by a considerable number of health authorities and PCGs. A newsletter from a prescribing adviser to a PCG was provided.

Trinity representatives did not imply that pharmacists were 'profiteering'. Notwithstanding that Trinity had already given an assurance to the NPA which it had hoped had been received in the positive spirit in which it was offered.

In summary Trinity submitted that it had not done anything which could be considered in breach of any aspect of the Code.

PANEL RULING

The Panel noted that page 4 of the booklet, headed 'Doesn't the chemist have to dispense the cheapest?', to which the NPA had specifically referred, stated, *inter alia:*

'There is no legal obligation for a pharmacist to dispense the least expensive version of any drug.'

and

'Any discount received by a pharmacist is not transferred to a GP's prescribing costs. In other words, additional profit for the pharmacist could mean additional cost to the surgery.'

The Panel noted that discounting was a long established part of wholesalers' and manufacturers' normal business practices. Pharmacists were able to negotiate discounts on purchases of medicines. The Prescription Pricing Authority (PPA) calculated reimbursement costs of the medicines dispensed according to the full NHS price of branded medicines or the Drug Tariff price for generic medicines. The overall benefit to the pharmacist of negotiating discounts was reduced by a system of claw back whereby a lump sum was deducted from the calculated reimbursement cost.

The Panel considered that the statement 'In other words, additional profit for the pharmacist could mean additional cost to the surgery' did not represent the whole picture. No mention had been made of the claw back. The booklet was too simplistic and in the Panel's view gave the impression that pharmacists could benefit directly from additional cost to the surgery. The Panel considered that the booklet was misleading in this regard. It was also disparaging to pharmacists. Breaches of Clauses 7.2 and 8.2 were ruled.

The Panel noted that the NPA also referred to Trinity staff accessing the prescriber's computer system and amending the medicine data base. The Panel did not consider that the NPA had complained about this activity and therefore it was not considered.

APPEAL BY TRINITY

Trinity stated that its appeal was based on its belief that the Panel had misinterpreted the nature of the arrangements regarding surgery prescribing costs and pharmacy reimbursement.

The Panel had argued that the claw back should be mentioned. Trinity disagreed. At a practice/PCG level the claw back had no relevance to the management of the practice/PCG prescribing budget. GP practices were charged with the full Tariff or list price of each item dispensed via the PPA.

The claw back which was deducted from the pharmacist's reimbursement was not credited to the practice. Indeed Trinity had checked with the Pharmacist Clawback Unit at the Department of Health (DoH) and had confirmation that no facility existed to enable practices to receive credit and that the claw back was taken as a saving to the DoH on a national basis only.

Thus the Panel's conclusion that Trinity 'had not told the whole picture' was not a reasonable conclusion – the claw back was irrelevant to the GP/PCG in terms of management of his/her budget.

Turning to the issue of Trinity's promotional message being disparaging to pharmacists – ie claiming that pharmacy profit could be at the cost of the GP budget, this was an undeniable fact in the specific area of sustained release (SR)/MR products in which Trinity made this claim. A GP prescribing an SR/MR product generically allowed the pharmacist to select which of the several options available the patient would receive. Being businessmen, pharmacists would be inclined to take into account, amongst other things, the profit available on the product selected.

Clearly the highest profit might well be on a product with the highest list price (Trinity had many examples should these be required). In this way the extra profit to the pharmacy was undeniably at the cost of the GP practice.

Trinity could not see how this could be seen as disparaging. It was simply an element of the reimbursement system. Trinity in no way sought to imply that the pharmacist would deliberately seek to increase a GP's costs, indeed Trinity had every sympathy with the need of the pharmacist to run a profitable business. Trinity did, however, maintain its right to explain to GPs/PCGs that in this particular area (SR/MR products) the usual blanket message of 'write generically to save costs' did not work.

* * * * *

At the Appeal Board hearing Trinity's representative stated that the message could have been worded more subtly. The company would not use the point negatively and the document would be reprinted without the last sentence. The representative decided not to appeal the Panel's ruling of a breach of Clause 8.2 of the Code.

APPEAL BOARD RULING

The Appeal Board noted that the statement 'Any discount received by a pharmacist is not transferred to a GP's prescribing costs. In other words, additional profit for the pharmacist could mean additional cost to the surgery' was factual, accurate and not misleading. No breach of Clause 7.2 was ruled.

The appeal on this point was thus successful.

The Appeal Board noted that the representative had accepted the Panel's ruling of a breach of Clause 8.2 of the Code.

Complaint received **6 October 1999**

Case completed **27 January 2000**

CASE AUTH/947/10/99

DIRECTOR v BRISTOL-MYERS SQUIBB

Presentation at a meeting

A cardiologist complained about what an independent speaker had said at an educational meeting organised by Bristol-Myers Squibb. The complainant alleged that a presentation entitled 'Are all statins the same?' contained material almost identical to that which had been used in a previous promotional campaign for Lipostat (atorvastatin). The complainant understood that complaints about the campaign had been upheld and that Bristol-Myers Squibb had had to modify it.

As the complaint involved a possible breach of undertaking the matter was taken up by the Director as the Authority itself was responsible for ensuring compliance with undertakings.

The Panel noted that a previous complaint had involved a 'Dear Doctor' letter which had stated that unlike other statins Lipostat metabolism was independent of cytochrome P450. The letter went on to refer to potential interactions of the other statins due to cytochrome P450 interactions. The impression from the letter about the potential interactions was misleading in the light of detailed information in the summaries of product characteristics (SPCs). No mention was made of the clinical significance of the interactions; some were just theoretical possibilities. Readers would not be able to judge the significance of the interactions from the letter. The Panel had ruled that the letter was misleading with respect to potential interactions and disparaging of the other statins.

With regard to the current case Bristol-Myers Squibb provided a number of slides which touched upon the matters considered in the previous case. The slides were not the same as the 'Dear Doctor' letter previously at issue. The Panel considered, however, that one slide in particular, which gave details of enzyme mediated drug interactions with fluvastatin, was misleading in light of the Lescol SPC; interactions with the medicines shown were a theoretical possibility, the clinical significance of which was not known. The Panel considered that the impression conveyed by the slide was sufficiently similar to that created by the material in the previous case for it to be caught by the undertaking given in that case. Breaches of the Code were ruled which were appealed by Bristol-Myers Squibb.

Upon appeal the Appeal Board appreciated the difficulties for companies asking independent speakers to present at educational meetings. It would be unsatisfactory for companies to dictate to speakers what they should present. Nevertheless, depending on their degree of involvement in the meetings, companies might have to ensure compliance with the Code. If this were not so then companies could employ independent experts to say what they, as companies, could not. No judgement would be made with regard to the professional integrity of a speaker. It was not a question of what a speaker said, it was a question of whether it was appropriate for the company to have sponsored the presentation.

The Appeal Board noted that Bristol-Myers Squibb had initiated the meeting, invited the speaker and provided him with the title of the presentation. Although the company stated that it had no prior knowledge of the content of the slides the speaker had spoken at previous Bristol-Myers Squibb meetings and so his general views would be known. The Appeal Board noted that the meeting had been granted PGEA approval and that the letter of invitation, signed by an area business manager, made it clear that the meeting was sponsored by Bristol-Myers Squibb.

Overall the Appeal Board considered that given Bristol-Myers Squibb's involvement with the meeting it was responsible for what the speaker said. The Appeal Board considered that the slide detailing interactions with fluvastatin was misleading and upheld the Panel's ruling of a breach of the Code. On balance the Appeal Board considered that the slides were different to the material considered in the previous case. The information had been used in a different context. The Appeal Board did not consider that the slides were caught by the undertaking given in the previous case and no breach of the Code was ruled in that regard.

A cardiologist complained about a presentation entitled 'Are all statins the same?' which had been delivered at a meeting, 'Getting to the Heart of the Matter', organised by Bristol-Myers Squibb Pharmaceuticals Limited. Bristol-Myers Squibb co-promoted a statin, Lipostat (pravastatin), with Sankyo Pharma UK Ltd. Bristol-Myers Squibb had organised the meeting; Sankyo representatives had been present at it but the company had not been directly involved with its organisation. The matter was thus not taken up with Sankyo.

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

COMPLAINT

The complainant stated that the background to this complaint was that earlier in the year Bristol-Myers Squibb ran an advertising campaign based primarily on the fact that Lipostat was not metabolised by the cytochrome P450 system as many of the other statins were. The major thrust of this campaign was to highlight the potential of serious life-threatening interaction with other medicines that were cytochrome P450 inhibitors. One of the medicines referred to was mibefradil, which, at the time, had just been withdrawn. The complainant understood that a number of people complained about this advertisement and he had telephoned Bristol-Myers Squibb at the time to register his own complaint. It

was also the complainant's understanding that some of these complaints were upheld and that the company was told to modify this particular campaign.

At the above meeting the presentation in question was given by a consultant physician. He showed a slide which was almost identical to the graphic used in the original advertising campaign, and indeed contained a reference to mibefradil which had been withdrawn. The complainant spoke to the representatives from Bristol-Myers Squibb who were present at the meeting about the matter and was told they had no control over material that was shown by invited speakers. However, as was reasonably common practice, the complainant had on a number of occasions been asked to show certain slides – particularly by the marketing departments of pharmaceutical companies. The complainant clearly found this unacceptable and had always refused to do so. The complainant alleged that the representatives were being economical with the truth, because he had definite information that some of the consultant physician's slides, including the one that he showed, were in the possession of BMS College.

It was the complainant's personal opinion that this type of action on the part of Bristol-Myers Squibb was a way of continuing an ill-thought out advertising campaign by way of getting speakers to show the same material that had originally been complained about. It was not the complainant's intention to criticise the senior management of the company, nor indeed the sales force, as the complainant personally believed that the problem lay within the marketing department.

RESPONSE

Bristol-Myers Squibb gave details about the arrangements for the meeting. A copy of the letter of invitation to the meeting, the programme, and a copy of the slides referred to by the complainant were provided. The slide it was believed that the complainant was referring to made no mention of mibefradil and therefore five slides which mentioned cytochrome P450 and potential drug-drug interactions were provided. The letter sent to attendees to confirm travel and accommodation details and the letter confirming PGEA approval for the meeting were also provided. No handouts were provided at the meeting, nor was any report of the meeting sent to attendees subsequently.

The meeting was attended by approximately 45 general practitioners and the six speakers, of whom four were hospital consultants. With regard to the presentation in question, Bristol-Myers Squibb stated that the speaker was widely known for his work with statins.

The slides shown at the meeting, including the slides that were being complained about, represented the speaker's own personal views. They were not produced by Bristol-Myers Squibb and therefore could not be construed to be an attempt by the company of continuing an ill-thought out advertising campaign by way of getting speakers to show the same material that had originally been complained about, as alleged by the complainant.

Bristol-Myers Squibb stated that the complainant alleged that the consultant physician showed a slide which included a graphic that was almost identical to the graphic which was used in the company's previous 'Dear Doctor' letter (LIP 288), which was the subject of the ruling referred to above (Cases AUTH/776/10/98 and AUTH/777/10/98). However, there were important differences between the graphic presented at the meeting and that in the mailing:

- The graphic on the slide showing the route of statin metabolism was wholly correct and made it clear which cytochrome P450 isoenzyme metabolised each of the statins. This addressed an area of concern in the breach ruling in relation to the previous cases, relating to the 'Dear Doctor' letter.

- The presentation included information on clinically significant interactions based on a literature review. The interactions presented were not just theoretical possibilities.

- The meeting was clearly intended to be an educational meeting. The programme was designed to allow discussion of the topics presented and to allow delegates, in discussion with the speaker, to formulate judgements about the significance of the interactions discussed. It was worth noting that the discussion on metabolism and interactions made up only a small part of a more general presentation.

Bristol-Myers Squibb was unable to agree with the complainant that use of the slides by an independent speaker at a PGEA approved meeting was an attempt by Bristol-Myers Squibb to continue an advertising campaign which had been previously found in breach of the Code. Since the content of the slides, their origin with an independent clinician (rather than Bristol-Myers Squibb), and the context in which they were used were all very different from the case in which Bristol-Myers Squibb was found in breach, it had not failed to comply with the previous undertaking, nor had it brought discredit to or reduced confidence in the pharmaceutical industry. Consequently there was no breach of either Clause 21 or Clause 2 of the Code.

Bristol-Myers Squibb provided a copy of a letter from the consultant physician about his presentation. He stated that he accepted lecturing invitations from commercial bodies on the strict condition that he was entirely free to present and interpret scientific data. He received no instructions from Bristol-Myers Squibb relating to the content of the lecture. He was provided with a title for the lecture. He had spoken previously at Bristol-Myers Squibb meetings and the company had material that had previously been used. The slides on drug interactions distinguished between the cytochrome P450 isoenzymes and detailed some of the more common potential interactions relevant to clinical practice. The case of mibefradil was highlighted as an example of a clearly important interaction with simvastatin. The slides were fully referenced to the literature.

PANEL RULING

The Panel noted that Bristol-Myers Squibb and Sankyo had been ruled in breach of the Code in Cases

AUTH/776/10/98 and AUTH/777/10/98. The material at issue then was a 'Dear Doctor' letter headed 'Lipostat – low potential for drug interactions'. The letter stated that, unlike other statins, Lipostat metabolism was independent of cytochrome P450 and went on to refer to potential interactions of the other statins due to cytochrome P450 interactions. The impression from the letter about the potential interactions of the other statins was misleading in the light of detailed information in their summaries of product characteristics (SPCs). No mention was made of the clinical significance of the interactions. Some were just theoretical possibilities. Readers would not be able to judge the significance of the interactions from the letter. The Panel had ruled that the letter was misleading in breach of Clause 7.2 with respect to potential interactions and disparaging of the other statins in breach of Clause 8.1 and the companies had provided the requisite undertakings.

Turning to the case now before it, the Panel noted that Bristol-Myers Squibb had approached the speaker and asked him to present at the meeting it had organised; the company had provided the speaker with the title of the presentation. The speaker was, as with any clinician, entitled to hold his own views and to express them. No judgement was being made in relation to the professional integrity of the speaker. It would be inappropriate for companies inviting speakers to meetings to control the content of their presentations. To do so would detract from the value of industry sponsored meetings. However, it was not possible for a company to completely dissociate itself from the content of meetings which it sponsored especially where the meetings were initiated by the sponsoring company.

The Panel considered that the five slides provided by Bristol-Myers Squibb were not the same as the 'Dear Doctor' letter previously at issue.

The first slide headed 'Metabolism of Statins: Major Cytochrome P450 Isoenzymes' showed the statins metabolised by CYP 450 3A4 (atorvastatin, cerivastatin, lovastatin, and simvastatin) and the statins metabolised by CYP 459 2C9 (fluvastatin, cerivastatin). This slide also showed that pravastatin was not metabolised by cytochrome P450.

The second slide headed 'CYP3-A4 Mediated Drug Interactions with Statins' showed that atorvastatin, cerivastatin, lovastatin and simvastatin were all metabolised by cytochrome P450 3A4. Medicines known to inhibit or compete for the same enzyme were listed, those being ketoconazole, erythromycin, diltiazem, mibefradil, itraconazole, grapefruit juice and 'others'. The inference of the slide was that if any of the four statins were co-administered with any of the other medicines then the result would be increased plasma levels of the statins. The clinical significance of this with regard to atorvastatin and cerivastatin was not stated although the slide showed that as a consequence rhabdomyolysis had been reported with lovastatin and simvastatin.

The Panel noted that, with regard to possible interactions with P450 3A4 inhibitors, the SPCs for the four statins differed (ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1999-2000). The SPC for Zocor (simvastatin) stated that it was metabolised by cytochrome P450 isoform 3A4 and that certain medicines had a significant inhibitory effect at therapeutic doses on this metabolic pathway. These medicines included cyclosporin, mibefradil, itraconazole, ketoconazole and other fungal azoles, erythromycin, clarithromycin and nefazodone. The concomitant use of these medicines led to an increased risk of rhabdomyolysis. The SPC for Lipobay (cerivastatin) stated that interaction studies with P450 3A4 inhibitors (erythromcycin, itraconazole, cyclosporin) had not been performed and advised caution when co-prescribing these products. The SPC for Lipitor (atorvastatin) stated that the medicine was metabolised by P450 3A4 and advised caution when it was administered with either inhibitors of the enzyme (eg macrolide antibiotics and azole antifungals) or with medicines metabolised by P450 3A4. The Panel noted that lovastatin was not available in the UK.

The third slide headed 'CYP2-C9 Mediated Drug Interactions with Fluvastatin' stated that the plasma levels of diclofenac, phenytoin, tolbutamide and warfarin would increase in patients taking fluvastatin.

The Panel noted that the SPC for Lescol (fluvastatin) referred to *in vitro* findings showing a potential effect of fluvastatin on the activity of the P450 CYP2C sub-family indicating a theoretical possibility of an interaction with medicines also metabolised by this sub-family such as warfarin, sulphonylureas [eg tolbutamide] diclofenac and phenytoin, if co-administered with fluvastatin although the clinical significance was unknown. The SPC noted that an *in vitro* study with warfarin showed that fluvastatin had no effect on prothrombin times or warfarin blood levels.

The fourth slide headed 'Potential for Clinically Significant Cytochrome P450 Drug Interactions' ranked the statins and gave details of the CYP isoenzyme.

The fifth slide headed 'Importance of Drug Interactions' stated that the combination of diltiazem 240mg plus simvastatin 40mg might give simvastatin concentrations equivalent to a 160mg dose of simvastatin alone. This slide also stated that diltiazem plus erythromycin plus simvastatin 40mg might give simvastatin plasma concentrations equivalent to a dose of 320mg of simvastatin alone. This slide also posed the question 'Would you willingly prescribe an 8-fold overdose to your patients?'

The Panel examined the Lipostat SPC which stated that no clinically significant effects were seen in a range of interaction studies. There was no mention of cytochrome P450.

The Panel considered that although the speaker was an independent physician, Bristol-Myers Squibb had facilitated his attendance at the meeting. It was therefore not possible for Bristol-Myers Squibb to totally dissociate itself from what he had said. If Bristol-Myers Squibb were not responsible then the effect would be for companies to use independent experts as a means of avoiding the restrictions in the Code.

The Panel considered that the impression from the third slide about potential interations with fluvastatin was misleading in the light of the details in the Lescol SPC; interactions with the medicines shown were a theoretical possibility the clinical significance of which was not known. The Panel ruled a breach of Clause 7.2 of the Code.

The Panel considered that the misleading impression conveyed by the third slide about potential interactions with fluvastatin was sufficiently similar to the impression created by the material at issue in Cases AUTH/776/10/98 and AUTH/777/10/99 which had been ruled in breach of the Code. It was thus caught by the undertaking given in that case. The Panel therefore ruled a breach of Clause 21 of the Code.

The Panel did not consider that the circumstances were such as to justify a ruling of a breach of Clause 2 of the Code which was used as a sign of particular censure. The material was not exactly the same as in the previous case and the circumstances were different. The Panel therefore ruled no breach of Clause 2 of the Code.

APPEAL BY BRISTOL-MYERS SQUIBB

Bristol-Myers Squibb noted that the Panel had confirmed that the five slides it had provided were not the same as the 'Dear Doctor' letter previously found in breach of the Code. In the Panel's view one of the slides (Slide 3 headed 'CYP 2C9 Mediated Drug Interactions with Fluvastatin') was in breach of Clause 7.2 of the Code. This was on the basis that the interaction of fluvastatin with the medicines shown was a theoretical possibility, the clinical effect of which was not known. The Panel's view was that because Bristol-Myers Squibb had facilitated the meeting, at which the slides were presented by an independent speaker, it was not possible for Bristol-Myers Squibb totally to dissociate itself from what the speaker had said. Slide 3 was caught by the undertaking given in the case of the 'Dear Doctor' letter and consequently a breach of Clause 21 was ruled.

Content of slide 3

Bristol-Myers Squibb's reiterated that the slide that was found in breach was not a Bristol-Myers Squibb slide, but was in fact one of the speaker's own. A copy of a letter from the speaker confirming this to be the case was provided. Bristol-Myers Squibb was unable to agree with the Panel that the interaction of fluvastatin with the medicines shown was a theoretical possibility, the clinical effect of which was not known. The speaker's slide was referenced to an *in vivo* study showing that fluvastatin inhibited the metabolism of diclofenac and also an *in vitro* study in man from which it was concluded that the plasma levels of the medicines listed increased. The clinical effect was the change in pharmacokinetics demonstrated to occur when the medicines listed were given with fluvastatin with a consequent increase in plasma levels. The speaker's slide was therefore not misleading and was not in breach of Clause 7.2 of the Code.

Context in which the slide was used

It was important to reiterate that the meeting at which the slides were presented was educational. This was confirmed by the fact that it was granted PGEA approval. While Clause 19.1 of the Code permitted companies to sponsor such meetings, it was less clear about the level of censorship they should exercise over the content of presentations given by independent experts. It was Bristol-Myers Squibb's belief that independent experts must be free to express their views at such educational meetings, as long as they allowed ample time for the issues presented to be fully debated by their audience. The free exchange of ideas and personal viewpoints among clinicians was an important aspect of their continuing education and contributed to the development of best medical practice.

The ruling of the Panel effectively restricted the independence of speakers at company sponsored meetings to express their own personal views. If the sponsoring company had to insist on reviewing all materials independent speakers wished to use, this would give the impression (whether justified or not) that the company was having undue influence over the material presented. This in turn might lead to a loss of confidence by the medical profession in the ability of the pharmaceutical industry to support in an unbiased way the provision of medical education.

The slides presented by the consultant physician were not provided by Bristol-Myers Squibb, but were his own and reflected his own personal views. The programme for the meeting allowed opportunity for the issues raised by the speakers to be fully debated by the audience. In the case of the slides at issue, a view opposing that of the speaker in relation to the significance of cytochrome P450 mediated interactions was expressed. In a letter thanking Bristol-Myers Squibb for arranging the meeting (a copy of which was provided) one of the GP delegates, made reference to this exchange of views. Clearly in the case of this meeting, physicians were exposed to a full and frank debate of the issues raised by the speakers.

Implicit in the ruling of the Panel was an assumption that Bristol-Myers Squibb might have taken advantage of the meeting to 'use independent experts as a means of avoiding the restriction of the Code'. This appeared to be the basis for the rulings of breaches of Clauses 7.2 and 21 of the Code. Bristol-Myers Squibb did not accept any suggestion that it used the meeting to get around the Code.

- In his letter, the GP congratulated Bristol-Myers Squibb on the impartial nature of the information presented by speakers at the meeting and the absence of any bias towards its products.

- The speaker had confirmed that the slides he showed were his own and represented his own personal views.

- Ample time was given and used to debate the topics raised by speakers at this meeting.

It was therefore difficult to conclude that Bristol-Myers Squibb had a hidden agenda for the meeting, as implied by the complainant and upheld by the Panel. On the basis that Bristol-Myers Squibb did not

use an independent expert at the meeting to avoid restrictions of the Code, breaches of Clauses 7.2 and 21 ruled by the Panel were not warranted.

APPEAL BOARD RULING

The Appeal Board noted that the degree to which pharmaceutical companies were involved with educational meetings would differ. At one extreme a meeting could be sponsored through an independent third party whereby a company did no more than provide funds to cover expenses. In such circumstances it was difficult to see that a company could be held responsible for what speakers said at the meeting. At the other extreme a company could initiate a meeting, choose the speakers and brief them as to what they should say, provide slides for the speakers and choose and invite the delegates. In such circumstances the Appeal Board considered that a company would be responsible for what speakers said. The whole proceedings of the meeting would be subject to the Code. If this were not the case then a company could employ independent experts to say what it, as a company, could not say, and so avoid the restrictions of the Code. Companies would normally be aware in advance of the general views of speakers they invited to present at meetings. In determining whether a pharmaceutical company was responsible for what was said at a meeting, particularly when its involvement was neither at one extreme or the other, then the whole of the arrangements would have to be considered including, *inter alia*, who initiated the meeting and chose the subject, who chose and invited the speakers, whether the speakers were briefed by the company and who chose and invited the delegates. Each case would have to be considered on its own merits.

The Appeal Board fully appreciated the difficulties for companies asking independent speakers to present at such meetings. It would be unsatisfactory for companies to dictate to speakers what they should present. On the other hand, depending on the degree of involvement, companies might have to ensure compliance with the Code. It could clearly be difficult to achieve the right balance in these regards. No judgement would be made as to the professional integrity of a speaker. It was not a question of what the speaker presented it was a question of whether it was appropriate for the company to have sponsored the presentation.

In the case now before it the Appeal Board noted Bristol-Myers Squibb's submission regarding the independence of the speaker, the nature of the meeting, that the slides presented by the speaker were his own and reflected his personal views.

The Appeal Board noted that the company had initiated the meeting, invited the consultant physician to speak and provided him with the title of the presentation. Whilst the company stated that it did not have prior knowledge of the content of the slides used at the meeting, the speaker had spoken at Bristol-Myers Squibb meetings before and so the company would be aware of his general views. The Appeal Board further noted that the meeting had been granted PGEA approval and that the letter of invitation, headed 'Invitation to BMS/Sankyo Pharma Symposium', had been signed by an area business manager from Bristol-Myers Squibb.

Overall, the Appeal Board considered that given Bristol-Myers Squibb's involvement it was responsible for the content of the presentation. The Appeal Board noted that no judgement was being made in relation to the professional integrity of the speaker.

The Appeal Board examined the five slides at issue. The Appeal Board noted that the third slide headed 'CYP2-C9 Mediated Drug Interactions with Fluvastatin' failed to explain the clinical significance of stated interactions between fluvastatin and stated medicines. The Appeal Board considered that the third slide was misleading and upheld the Panel's ruling of a breach of Clause 7.2 of the Code. The appeal in this regard was unsuccessful.

The Appeal Board noted that the second slide headed 'CYP3-A4 Mediated Drug Interactions with Statins' listed mibefradil as a medicine known to inhibit or compete for cytochrome P450 3A4. The complainant had alleged that the second slide was similar to the material ruled in breach of the Code in Cases AUTH/776/10/98 and AUTH/777/10/98. The second slide did not state the clinical significance of co-administration of atorvastatin and cerivastatin with any of the medicines listed. The Appeal Board noted that no specific ruling had been made by the Panel with regard to the second slide and it was not therefore subject to appeal. The Appeal Board was nevertheless concerned that the slide was misleading and requested that Bristol-Myers Squibb be so advised.

The Appeal Board considered that, on balance, the slides at issue were different to the material considered in Cases AUTH/776/10/98 and AUTH/777/10/98. The information had been used in a different context. The Appeal Board did not consider that the slides were caught by the undertaking given in the previous case. No breach of Clause 21 was ruled. The appeal in this regard was thus successful.

Complaint received **25 October 1999**

Case completed **31 March 2000**

GENERAL PRACTITIONER v MERCK SHARP & DOHME

Cancelled meeting

A general practitioner complained that he had not been informed about the cancellation of a meeting sponsored by Merck Sharp & Dohme even though he had spoken to the third party responsible for organising it to confirm his attendance. He had gone to the venue only to be told that the meeting had been cancelled.

The meeting had been organised by a local postgraduate tutor and it was he who was responsible for its cancellation; his secretary had no recollection of any contact with the complainant. Merck Sharp & Dohme was to have paid the costs of the speakers and chairman plus the costs of the refreshments and had declared its sponsorship on the invitation. The Panel considered that on balance, despite the administration having been undertaken by a third party, Merck Sharp & Dohme was responsible for the meeting.

The Panel observed that the parties' accounts differed and there was no documentary evidence to support either account. It was difficult to determine precisely what had transpired but the Panel accepted that extreme dissatisfaction was necessary on the part of an individual before he or she submitted a complaint. A judgement had to be made on the available evidence. The Panel was concerned about the inconsistencies between the parties' accounts but decided to rule no breach of the Code.

COMPLAINT

A general practitioner complained that he had not been informed about the cancellation of a meeting which had been sponsored by Merck Sharp & Dohme Limited. Details of the meeting, at which two consultants were to speak, were given on an A4 sheet which stated that the meeting was sponsored by Merck Sharp & Dohme. General practitioners had been invited to respond by posting the tear-off slip on the invitation to the organiser's secretary or by telephoning her. The complainant stated that he had left a message on the secretary's answerphone; she had called back and the complainant had told her that he would be attending and in fact she had encouraged him to attend such meetings without formally returning the tear-off slip or prior telephoning. He had gone to the venue only to be told that the meeting had been cancelled long ago. This had left him surprised and disappointed.

The complainant stated that he had immediately sent a complaint to Merck Sharp & Dohme in response to which the company's national sales manager had denied any involvement in the issue of invitations and added that not Merck Sharp & Dohme, but the local postgraduate tutor had cancelled the meeting and hence Merck Sharp & Dohme was not responsible for this. The complainant took the opposite view and considered that, as sponsor, Merck Sharp & Dohme had the responsibility to find out who was to attend to ensure that information about the cancellation was conveyed to them. This had not been done.

RESPONSE

Merck Sharp & Dohme stated that the meeting was organised by the local postgraduate tutor and that his secretary had handled all administration in relation to it.

Merck Sharp & Dohme's involvement was limited to a contribution towards the catering costs associated with the meeting. The company had no further involvement in the organisation of the meeting.

The offer to make a contribution to the catering costs was a local representative initiative. The representative involved had subsequently left the company before the date of the meeting and another oversaw Merck Sharp & Dohme's involvement. Both representatives had passed the ABPI's medical representatives' examination.

Merck Sharp & Dohme's sponsorship of the meeting was included in the invitation produced by the postgraduate centre in order to comply with Clause 9.9 of the Code.

The complainant alleged that he contacted the organiser's secretary, in mid June, confirming his interest in attending the meeting. When Merck Sharp & Dohme first received his complaint, in mid July, the representative made some enquiries with the postgraduate centre. There seemed to be some conflict between the accounts of the complainant and the secretary. The postgraduate tutor decided to postpone the meeting due to a disappointing level of interest in it. The secretary did not recall having had any contact with the complainant; she did not, therefore, contact him to let him know that the meeting would no longer take place.

The representative spoke to the complainant and offered to see him at a lunchtime to cover the therapeutic areas that would have been addressed in the meeting. The complainant declined and stated that he wished to persist with his claim for compensation from Merck Sharp & Dohme.

Merck Sharp & Dohme's view was that the regrettable breakdown in communication was ultimately a matter between the complainant and the postgraduate centre. There was a series of communications between the complainant and the company's national sales manager. Another offer was made to send a representative to cover the therapeutic areas.

Merck Sharp & Dohme did not accept the complainant's argument that by including the company's sponsorship in the invitation (in order to

comply with Clause 9.9) the company became responsible for all organisational details of the meeting. Merck Sharp & Dohme accepted that it was responsible for the aspects of the meeting relating to its sponsorship, commensurate with its level of involvement in, and control of, the meeting (such as level and acceptability of hospitality, etc.). Merck Sharp & Dohme thought it rather unfair, however, that this should render it liable for all administrative aspects of the meeting. In any event, the situation had arisen purely as a result of a genuine misunderstanding between the complainant and the secretary and Merck Sharp & Dohme did not, therefore, believe a breach of the Code had occurred.

Merck Sharp & Dohme provided a copy of a letter from the postgraduate tutor; this confirmed that he had cancelled the meeting and that his secretary had so informed those who had replied. The postgraduate tutor undertook responsibility for publicity for the meeting and receipt of the replies. Merck Sharp & Dohme had agreed to pay the speakers' remuneration and the cost of refreshments for participants.

Following requests for further information Merck Sharp & Dohme provided details of the anticipated costs of the meeting. The company explained that the representative would have approached the postgraduate tutor in the first instance to discuss potential therapeutic areas that that he might be interested in covering. The meeting itself would have been non-promotional, covering the disease area only. No promotional material would have been displayed although the representative would have attended. Merck Sharp & Dohme stated that the crux of the issue was who should be held responsible for the administration of the meeting. The postgraduate tutor accepted that it was his responsibility and that was also Merck Sharp & Dohme's understanding. There was no reason under the Code to prevent the allocation of responsibilities as occurred between Merck Sharp & Dohme and the tutor.

PANEL RULING

The Panel considered that this case was difficult because the extent of Merck Sharp & Dohme's involvement was unclear. This was partly due to the fact that the meeting had not taken place. It was possible for pharmaceutical companies to sponsor meetings and have no involvement other than contributing to the costs. Such arrangements had to meet the requirements of the Code.

The Panel noted the submission from Merck Sharp & Dohme that it was not responsible for the administration of the meeting. The Panel noted that the company approached the course organiser to discuss potential therapeutic areas. Merck Sharp & Dohme was to pay the costs of the speakers and chairman plus the cost of refreshments and had declared its sponsorship on the invitation. The Panel noted that the administration had been undertaken by a third party and the third party had cancelled the meeting. The third party believed that everybody who had replied to the invitation had been informed that the meeting had been cancelled and his secretary did not recall having had any contact with the complainant. The Merck Sharp & Dohme representative and the national sales manager had contacted the complainant about the matter.

The Panel considered that on balance, despite the administration having been undertaken by a third party, Merck Sharp & Dohme was responsible for the meeting.

The Panel observed that the parties' accounts differed and there was no documentary evidence to support either account. It was difficult in such circumstances to determine precisely what had transpired. The Panel accepted that extreme dissatisfaction was necessary on the part of an individual before he or she submitted a complaint. A judgement had to be made on the available evidence. The Panel was concerned about the inconsistencies between the parties' accounts but decided to rule no breach of Clauses 9.1, 15.2 and 15.4 of the Code.

Complaint received **20 November 1999**

Case completed **14 February 2000**

CASE AUTH/956/11/99

LILLY v JANSSEN-CILAG

Promotion of Risperdal

Lilly complained about a leavepiece for Risperdal (risperidone) issued by Janssen-Cilag. The leavepiece detailed a study in Canada by Procyshyn *et al* which aimed to compare usage costs, patterns and clinical outcomes associated with the use of risperidone and olanzapine in a hospital setting. The study was a retrospective chart review of patients who had received either risperidone or olanzapine as their first new medicine after reassessment. The study concluded that treatment with risperidone was associated with lower cost and was more effective than olanzapine. By applying these results to the UK it was stated in the leavepiece that prescribing Risperdal in preference to olanzapine could mean a saving of more than £1400/year/responding patient. Olanzapine was Lilly's product Zyprexa. Janssen-Cilag stated that the data was used as an adjunct to the main promotional campaign which promoted switching from older conventional antipsychotics. A Powerpoint presentation had also been prepared.

Lilly had a number of concerns about the data. It considered it was unlikely that the two groups of patients assessed were comparable as it was likely that olanzapine had been given to the sickest patients and those who had failed on other therapies, including risperidone. Patient data had been quoted sequentially but this would not prevent patient groups from being different at baseline and would not prevent selection bias. Many of the conclusions were based on chart data but it was unclear to Lilly how systematic had been the extraction of information from the charts. The economic evaluation assessed inpatient medication costs only over a short time period, a maximum of 120 days. At least six months was needed to assess the economic impact of pharmacotherapy. Lilly was also concerned at the high dose of olanzapine used which suggested a greater severity of illness in patients treated with it.

The Panel noted that the study was retrospective and non-randomised and that there was no control group. The authors themselves acknowledged that the study's most obvious limitation was that it was unmasked and non-randomised. They considered that they had corrected for the major source of bias. Adjustments in analysis of the data were made in relation to certain variables, prior use of atypical antipsychotics and prior use of risperidone. No adjustments were made for the primary variable, cost per responding patient. The Panel was concerned that selection bias could not be eliminated by subsequent statistical analysis. The Panel understood that bias was almost always inherent in retrospective studies. The data were collected from charts in which doctors recorded whatever they considered to be significant. No objective rating scales were used to determine efficacy, which was acknowledged by the authors to be another major limitation of the study. The Panel was also concerned about the extrapolation of 120 days' hospital treatment data to give an annual saving for patients in the community. The Panel noted that the mean dose of olanzapine for responders was 17.19mg per day. The mean daily dose of olanzapine was 19.83mg which was considerably higher than the 12.6mg suggested by the data from UK psychiatry prescribing, the 10.77mg suggested by IMS data, or the 13.2mg mean modal dose in the major registration study for olanzapine. Olanzapine had only just been introduced in Canada when the study started. The authors of the study acknowledged that this might have had an impact on the study outcomes since doctors might have been unfamiliar with the use of the product. The data was based on only 30 patients in each treatment group.

The Panel noted that the leavepiece gave details of the study on a page headed 'Study Design'. No comment was made regarding the limitations of the study. The results of the study had been applied to UK practice. The Panel considered that overall the leavepiece was misleading given its concerns noted above. A breach of the Code was ruled which the Panel considered also applied to the Powerpoint presentation.

Eli Lilly & Company Limited complained about promotional material for Risperdal (risperidone) issued by Janssen-Cilag Ltd. The material at issue referred to a poster headed 'Drug utilization patterns and outcomes associated with in-hospital treatment with risperidone and olanzapine' Procyshyn RM *et al*, Riverview Hospital British Columbia. The poster was presented at the American Psychiatric Association Meeting in 1998. Lilly marketed Zyprexa (olanzapine).

The study aimed to compare usage costs, patterns and clinical outcomes associated with the use of risperidone and olanzapine within a hospital setting. The study was a retrospective chart review of patients on the ward who received either risperidone or olanzapine as their first new medicine after re-assessment. There were 30 patients per group and the data was collected to a maximum of 120 days. Responders were defined as patients with a clinically significant reduction in symptoms related to their primary diagnosis who continued to take the medicine. A significantly greater number of risperidone treated patients responded to therapy (60%) compared to olanzapine (27%). Forty per cent of patients initially treated with risperidone were discharged from hospital on their original therapy compared to 13% of patients originally treated with olanzapine. The study concluded that with this cohort of patients, treatment with risperidone was associated with lower cost and was more effective compared to olanzapine.

Janssen-Cilag stated that the data was used as a reference for a single, study specific, leavepiece (603018). The data was used as an adjunct to the main promotional campaign which promoted switching from the older conventional antipsychotics. It was used in context and relevant to the recipients.

A Powerpoint presentation had also been prepared. The data was peer reviewed and published at the end

of 1998; soon after, in April 1999, representatives and managers were instructed not to use the leavepiece and to use supplied reprints of the peer reviewed paper in accordance with Clause 11.1 to discuss the data with interested clinicians or pharmacists. The Powerpoint presentation was continued for group presentations and revised in the light of the new reference. It was withdrawn in September 1999 in the light of the price reduction for olanzapine. At the time of the complaint the reprint was being provided to interested parties, clinicians, pharmacists and payors. The company was not otherwise using the data.

COMPLAINT

Lilly was concerned about a number of aspects of the data.

1 Selection bias

Lilly stated that due to the retrospective nature of this evaluation, it was unlikely that the two groups of patients assessed were comparable. At the time that the review was conducted, risperidone was approved as first line therapy and olanzapine as second line therapy in British Columbia. It was extremely likely that olanzapine was given to the sickest patients and patients who had failed on other therapies (including risperidone). This treatment resistant group would be more likely to need higher doses and would be less likely to respond to treatment than the less severely ill patients who were placed on risperidone.

Janssen-Cilag's reply was that data correction was performed for prior use of atypicals in the analysis. However, this would still not exclude selection bias at the patient level as doctors' perceptions of efficacy of one or other of the medicines could potentially be different. In the main cost analysis presented in the leavepiece the costs and outcomes used were not adjusted for any prior use since they were simple proportions and doses. Cost per responding patient had been calculated but adjustments had not been made to account for prior use of antipsychotics. The primary claim in the leavepiece (cost per responding patient) had therefore not been adjusted for prior atypical use.

2 Inadequate statistical contol for selection bias

Lilly stated that the authors attempted to negate the inherent selection bias in the study by gathering patient data sequentially and correcting for prior use of atypical antipsychotics and prior use of the comparator. Sequential patient selection would not prevent patient groups from being fundamentally different at baseline and, therefore, would not prevent selection bias. Prior use of atypical antipsychotics and/or the comparator agent did not indicate that one treatment group was more severely ill than the other. Therefore, controlling for these confounding factors did not adequately correct for baseline differences that existed between the treatment groups.

Janssen-Cilag replied that the abstract was accepted by APA 1998 and CINP 1998 Review Committees, but Lilly stated that it was unlikely that the full methodology was described in the abstract, so it could not strictly be said that this was 'reviewed'.

The baseline characteristics which were explored in the poster did not include prior use of atypicals. Only age, sex, duration of illness and diagnosis were compared and shown to have no significant differences. Thus although some analyses adjust for prior atypical use, there was no information on the baseline differences between groups.

3 Chart data

Lilly stated that many of the conclusions were based on chart review data. From the information presented it was unclear how systematic the investigators were in extracting information from the charts. Chart data was likely to vary greatly among patients and physicians. For example, Patient A might have achieved an identical response as Patient B, but Patient A might be labelled as a non-responder while Patient B was labelled as responder due to differences in how physicians documented response in patient charts. Retrospective assessments of clinical response should be carried out using a systematic criteria that was easily identified rather than relying on subjective review of chart information. Of course, the most valid approach to assessing clinical response would be carried out in the context of a prospective trial where a well accepted definition of response based on a valid efficacy measure (eg the PANSS) was established prior to the study initiation.

Lilly agreed with Janssen-Cilag's view that it was valuable to study drug utilisation in the 'real world' as a supplement to randomised clinical trials. Once again, however, it believed that retrospective chart evaluation and 'outcomes' based on individual clinicians' notes could still be biased. Since the study was unblinded, the outcome was not an objective one.

4 Medication cost focus

Lilly stated that the economic evaluation only assessed inpatient medication costs over a short time period (maximum of 120 days). To assess the economic impact of pharmacotherapy, total costs (inpatient, outpatient and medication costs) should be considered over a prolonged time period (at least six months). This was especially important in schizophrenia due to the impact of non-compliance and medication efficacy on relapse rates and cost. Failure to consider the total cost picture left the decision maker with a distorted and incomplete assessment of the economic impact of alternative therapies on the healthcare system. In addition, the study extrapolated cost data from the 120 days to 1 year, which assumed response and dose remained constant over one year (see below).

One of the major criticisms of this study was that it only looked at a snapshot of the time costs of schizophrenia. The cost of medication prescribed was only one (relatively small) piece of the total cost of the illness. Hospitalisation alone was a huge cost in itself and was not accounted for in this study. It was also unclear why an arbitrary cut off of 120 days was taken for evaluation of medication costs. Lilly did not know what the range was with regard to 'time to recovery' for each medicine.

In addition, Lilly disagreed with Janssen-Cilag's statement that 'the capitation calculation per patient year is common practice' in the context of a relapsing condition such as schizophrenia. If the cost for medicine was extrapolated out for one year then so should the outcomes be extrapolated, yet they were only considered up to 120 days.

Hospital in-patient doses ('acute' treatment doses) were also those which were extrapolated out to one year and the assumption that the doses would remain constant over this time was something that could not necessarily be assumed. The likelihood was that for both medicines doses might be reduced.

5 Doses

Lilly was also concerned that the mean daily dose of olanzapine used in this sample was 19.83mg. This was high and suggested, once again, a greater severity of illness in the olanzapine treated patients. In addition, data from UK psychiatry prescribing (from Psychotrack in May 1998) indicated that the average daily dose for repeat prescriptions of olanzapine was 12.6mg. Data from IMS regarding GP prescribing from last year to March 1998 revealed an average daily dose of olanzapine of 10.77mg. This would be what would be expected ie lower doses being used for long-term community prescribing. It was, therefore, unfair to extrapolate hospital in-patient doses out to one year when calculating the expected costs. It was also, especially in this type of patient group, likely that as response was only assessed up to a maximum of 120 days, that over a year further relapses could occur, even in those patients initially classed as responders. In order to accurately compare data for the two medicines, therefore, a longer term study should be carried out.

Janssen-Cilag replied that mean doses in the study were those to which patients 'responded'. Lilly would agree that both doses (5.8mg for risperidone and 19.8mg for olanzapine) were within the approved dose ranges in the marketing authorization for both products. However, Lilly would strongly disagree with Janssen-Cilag's comment that these doses were 'in line with the doses found to be most effective in randomised controlled trials'. For olanzapine mean modal doses in the major registration study of 1996 patients (Tollefson *et al* 1997) was 13.2mg / day.

Since the exchange of letters last year, Lilly stated that the full paper had been published. A letter challenging the data had been sent to the journal by Lilly. A reply by Procyshyn was also published. Copies were provided.

Janssen-Cilag had used the Procyshyn data in other countries and Lilly referred to adverse rulings made in Australia, The Netherlands and Finland.

Lilly stated that despite other jurisdictions ruling against this data, Janssen-Cilag persisted in using this and similar studies as major platforms of its campaign against olanzapine. Lilly was still finding the promotional piece in use by sales representatives. Lilly alleged that the continued use of this data was in breach of Clause 7.2 of the Code, and the study used was not in compliance with the Guidance on Good Practice in the Conduct of Economic Evaluation of Medicines (in particular sections 3 and 9).

RESPONSE

Janssen-Cilag objected to Lilly's reference to rulings on use of this data from other countries as it was selective, ie countries where complaints were not settled in their favour were not mentioned, and was potentially prejudicial. Janssen-Cilag therefore made the assumption that it would not have any bearing on the case in the UK and it did not intend to address it further.

Janssen-Cilag stated that the study in question was the first naturalistic study of its kind with the primary outcome being daily cost of treatment based on medicine utilisation in a 'real world' (non-clinical trial) setting. As could be seen the origins of the data (ie Canada) were clearly stated and the phrase 'implications for the UK' had been used in the leavepiece as an opportunity for a physician or pharmacist to discuss the findings against his / her own practice or experience. The patient type, setting and methodology used for the study were also stated clearly and the results presented as simple cost comparisons with pounds sterling substituted for Canadian dollars based on the mean daily doses (using prices from MIMS). Secondary endpoints looking at efficacy and tolerability were also performed to exclude the possibility of the greater efficacy or tolerability of one compound off-setting any cost difference found and this was exactly how the results were presented. All claims made within the leavepiece related to the study. The strength of the data was its simplicity and transparency in that if a clinician or pharmacist was aware of the average doses of each compound used then they could agree with or adjust the results as appropriate. If they were not aware then it provided an impetus to them to assess this for themselves. The main message was not that Risperdal was better than olanzapine but that given the differences in acquisition costs found in this and similar studies, and against a background of limited budgets in the NHS, Risperdal should be tried before olanzapine. The Powerpoint slide set was entirely based on the information given in the leavepiece.

Lilly had suggested that Janssen-Cilag was not in compliance with the Guidance on Good Practice in the Conduct of Economic Evaluations of Medicines. However, in Janssen-Cilag's view, compliance with this Guidance was not at issue here. Many perfectly acceptable and published studies did not comply and non-compliance was not relevant to adherence to the Code.

Since this data was first presented, numerous other studies had been conducted internationally to the same basic design including two UK sites. Kasper and Duchesne presented an abstract detailing the pooled results from eleven such studies at XI World Congress of Psychiatry in Hamburg in August 1999. This data from over six hundred evaluable patients from Germany, Austria, Australia, the Netherlands and Denmark, demonstrated a clear advantage for Risperdal over olanzapine on acquisition costs without any apparent compensation in greater

efficacy or tolerability on the part of olanzapine, ie these findings fully supported the data at issue.

The two major clinical trials comparing the two compounds (Tran *et al*, Conley *et al*) also demonstrated that on the main primary end points, Risperdal was at least as effective as olanzapine with similar side effect profiles. Olanzapine appeared to consistently have greater weight gain than Risperdal. Also if costs were applied to the mean modal doses compared then Risperdal was once again the cheaper product.

Janssen-Cilag submitted that the greater body of available evidence was supportive of the Procyshyn data and thus there was no breach of Clause 7.2. The data had been presented in a simple and transparent way; any claims made were appropriate and did not breach Clause 7.2.

PANEL RULING

The Panel noted Janssen-Cilag's comments about Lilly's reference to rulings in jurisdictions outside the UK, but considered that complainants could provide information from any source to support their complaint. Complaints were, however, judged in relation to the use of material in the UK and the requirements of the UK Code.

The Panel noted that Lilly alleged that the study was not in accordance with the Guidance on Good Practice in the Conduct of Economic Evaluations of Medicines. This Guidance was issued jointly by the Department of Health and the ABPI and while it was referred to in the Code, it was not for the Panel to judge the study against the Guidance. The Panel's role was to judge whether or not the use of the data was in accordance with the Code.

The Panel noted that the study was retrospective and non-randomised and that there was no control group. The authors themselves, in the published paper, acknowledged that the study's most obvious limitation was that it was unmasked and non-randomised. The authors considered that they had corrected for the major source of bias. The Panel noted that adjustments in analysis of the data were made in relation to certain variables, prior use of atypical antipsychotics and prior use of risperidone. No adjustments were made for the primary variable, cost per responding patient. The Panel was concerned that selection bias could not be eliminated by subsequent statistical analysis. The Panel understood that bias was almost always inherent in retrospective studies. The data were collected from charts in which doctors recorded whatever they considered to be significant. No objective rating scales were used to determine efficacy which was acknowledged by the authors to be another major limitation of the study. There was likely to be some subjective assessment. The Panel was also concerned about the extrapolation of 120 days' hospital treatment data to give an annual saving for patients in the community. In this regard the Panel noted Lilly's view that the disease was unlikely to remain stable over a one year period and thus treatment was also unlikely to remain stable.

The Panel noted that the mean dose of olanzapine for responders was 17.19mg per day. The mean daily dose of olanzapine was 19.83mg which was considerably higher than the 12.6mg suggested by the data from UK psychiatry prescribing, the 10.77mg suggested by IMS data, or the 13.2mg mean modal dose in the major registration study for olanzapine. It was also noted that olanzapine had only just been introduced in Canada when the study started. The authors of the study acknowledged that this might have had an impact on the study outcomes since doctors might have been unfamiliar with the use of the product. The Panel also noted that the data was based on only 30 patients in each treatment group.

The Panel noted that the Kasper and Duchesne abstract was published in September 1999; the abstract contained very little information. It consisted of pooled results of eleven studies conducted to the same design as the study at issue. Potentially it could suffer from the same limitations.

The Panel examined the six page leavepiece in question which highlighted the results of the Procyshyn study and the application of the results to the UK. The leavepiece stated that prescribing Risperdal in preference to olanzapine could mean a saving of more than £1400 a year per responding patient. The details of the study were given on a page headed 'Study Design'. No comment was made regarding the limitations of the study. The Panel considered that overall the leavepiece was misleading given its concerns noted above. A breach of Clause 7.2 of the Code was ruled. The Panel considered that this ruling also applied to the Powerpoint presentation.

The Panel noted that Janssen-Cilag stated that it was now only using the published paper in accordance with Clause 11.1 of the Code. The Panel queried whether this was so as it appeared that Janssen-Cilag was using the paper for detailing healthcare professionals. The Panel did not know exactly what use was made of the paper but requested that Janssen-Cilag should review its use in light of the Panel's ruling.

Complaint received **22 November 1999**

Case completed **1 March 2000**

CASE AUTH/958/11/99

ALLERGAN v PHARMACIA & UPJOHN

Xalatan leavepiece

Allergan complained about a leavepiece for Xalatan (latanoprost) eye drops issued by Pharmacia & Upjohn which was entitled 'Why switch to Xalatan monotherapy?' Allergan marketed Alphagan (brimonidine) eye drops.

A page headed 'Switch to Xalatan monotherapy … and it's only one drop per day' featured a bar chart which stated the range of drops per day associated with a number of timolol based treatment options. Timolol plus brimonidine, for example, required four drops per day and this was compared with Xalatan monotherapy which required one drop per day. Allergan alleged that this was an unfair comparison as it compared monotherapy with Xalatan with adjunctive therapy for other products. In addition, Allergan alleged that the bar chart implied at least equivalent efficacy of Xalatan to all the treatments compared but Allergan was not aware of any data to support this in relation to the timolol/brimonidine combination. The Panel noted that Xalatan was indicated in patients who were intolerant or insufficiently responsive to another intraocular pressure (IOP) lowering medication. Although Xalatan could be used after brimonidine monotherapy, in the Panel's view it would be more common to use it where combination therapy based on timolol had failed or was not tolerated. The Panel considered that the chart included those therapy options for which Xalatan would most commonly be substituted. No breach of the Code was ruled in that regard. The Panel noted that the page contained no reference to the relative efficacy of the therapies listed which were only compared in terms of the number of eye drops required each day. In the Panel's view, however, specifying four combinations suggested that Xalatan had equal efficacy to those particular combinations stated. There was no data to show that the efficacy of the product was equivalent to all of the stated combinations. The Panel considered that the chart was thus misleading and ruled a breach of the Code.

The claim 'Up to twice as effective as timolol in reaching target IOPs' appeared on two pages of the leavepiece, each time with the words 'twice as effective' appearing in red. Allergan alleged that only for target IOP ≤15mmHg could the claim 'twice as effective' be considered to be accurate (ratio of effectiveness 1.9), while for ≤16mmHg and ≤17mmHg, it would be more accurate to state 'one and a half times more effective' (ratio of effectiveness 1.5). Even this was not accurate for the remaining IOPs. Allergan accepted that the statement was 'up to twice as effective' but considered that the emphasis on 'twice as effective' in both instances made it likely that this was the message which would be conveyed to the reader. In the Panel's view the data showed that Xalatan-treated patients were up to twice as likely to achieve target IOPs than timolol-treated patients. There was no explanation, however, which would enable the reader to understand that the calculation of odds-ratios formed the statistical basis of the claim. In addition the Panel noted that '… twice as effective …' was printed in red and considered that most readers would only see that part of the claim and so miss the significance of the preceding words 'Up to …'. The Panel considered that the presentation of the data and the highlighting of part of the claim was misleading. A breach of the Code was ruled.

Allergan Ltd complained about a six page, folded leavepiece (ref P4411/4/99) for Xalatan (latanoprost) eye drops which had been issued by Pharmacia & Upjohn Limited. Xalatan was indicated for the reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma and ocular hypertension who were intolerant or insufficiently responsive to another IOP lowering medication. The leavepiece was entitled 'Why switch to Xalatan monotherapy?' and was used to promote the product to ophthalmologists.

Allergan marketed Alphagan (brimonidine) eye drops which could be used as monotherapy for the lowering of IOP in patients with open angle glaucoma or ocular hypertension, who were known, or thought likely, to be intolerant of topical betablocker therapy, and/or in whom topical betablocker therapy was contraindicated. Alphagan might be used as adjunctive therapy when IOP was not adequately controlled by a topical betablocking agent.

1 Page headed 'Switch to Xalatan monotherapy … and it's only one drop per day'

This page featured a bar chart which stated the range of drops per day associated with a number of timolol-based combination treatment options; treatment with timolol plus brimonidine required four drops per day. Treatment options which thus required the use of multiple eye drops per day were compared with Xalatan monotherapy which required one drop per day.

COMPLAINT

Allergan alleged that the bar chart gave an unfair comparison as it compared monotherapy with Xalatan with adjunctive therapy for the other products eg, timolol plus brimonidine, rather than brimonidine monotherapy.

In addition Allergan considered that the bar chart was misleading as it implied at least equivalent efficacy of Xalatan to all the treatments compared. While data were presented to support greater efficacy than timolol/pilocarpine combination, Allergan was not aware of any data to support equivalent efficacy of Xalatan and timolol/brimonidine combination. During the course of intercompany correspondence, Allergan accepted Pharmacia & Upjohn's argument that there was no specific reference to efficacy on the page, which directly referred only to convenience, but considered that the context of the figure made it likely that it would be considered to imply equivalent efficacy and noted that the facing page and the other previous pages dealt with efficacy. In addition the page in question was headed 'Switch to Xalatan monotherapy'; equivalent efficacy was usually presupposed in making a switch.

Allergan alleged a breach of Clause 7.2 of the Code.

RESPONSE

Pharmacia & Upjohn stated that it did not accept that the bar chart was misleading since it had merely taken 24 hour dosing regimens from MIMS. There was no attempt to discuss efficacy or efficacy comparisons on this page. The page served to outlined the fact that, if Xalatan monotherapy was used, only one drop per day was required in contrast to combination therapies. This was particularly important for glaucoma patients where use of multiple combination therapies could create considerable compliance problems. The bar chart did not have any markers of efficacy, did not purport to be a graph and was clearly entitled 'Number of drops per day'.

Pharmacia & Upjohn noted that the leavepiece dealt with efficacy on three facing pages; page 2 showed long term efficacy, page 3 showed target IOP data and page 4 showed efficacy versus a combination therapy. These three pages clearly outlined the efficacy message. The piece then went on to discuss dosage and compliance on a separate, clearly headed page which was a natural conclusion to the detail story as compliance was a significant issue for patients on combination therapy. The page in question was designed to show that when a patient was switched from the initial betablockers, the introduction of combination therapy would mean frequent dosing and multiple drop applications (from 2 up to 10 drops per day), whereas use of Xalatan monotherapy was only one drop per day.

Pharmacia & Upjohn did not consider that the page was misleading or in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that glaucoma was commonly first treated with a topical betablocker unless such medicines were contra-indicated. The British National Formulary stated that other medicines were added as necessary to control IOP. Xalatan was indicated in patients who were intolerant or insufficiently responsive to another IOP lowering medication. Xalatan was thus a second-line therapy and although it could be used after brimonidine monotherapy, in the Panel's view it would be more common to use it where combination therapy based on timolol had failed or was not tolerated. The Panel thus considered that the chart included those therapy options for which Xalatan would most commonly be substituted. No breach of Clause 7.2 was ruled in that regard.

The Panel noted that the page in question contained no reference to the relative efficacy of the therapies listed. The therapies were only compared in terms of the number of eye drops required each day. In the Panel's view, however, specifying four combinations suggested that Xalatan had equal efficacy to those particular combinations stated. The page was not about the convenience of Xalatan compared to multiple therapy generally. There was no data to show that the efficacy of the product was equivalent to all of the stated combinations. The Panel considered that the chart was thus misleading and ruled a breach of Clause 7.2 of the Code.

2 Claim 'Up to twice as effective as timolol in reaching target IOPs'

This claim appeared on two pages of the leavepiece, each time with the words 'twice as effective' appearing in red. The data on which the claim was based (Hedman 1997) was presented in a table on the second of these two pages. The table listed 6 target diurnal IOPs achieved at the end of 6 months' treatment (≤20mmHg to ≤15mmHg) and stated the percentage of patients on either Xalatan od (n=398) or timolol bd (n=318) achieving that target. In all cases a statistically significantly greater percentage of patients in the Xalatan-treated group achieved target IOP. The results for Xalatan and timolol respectively were: ≤20mmHg, 89%, 81%; ≤19mmHg, 83%, 72%; ≤18mmHg, 70%, 55%; ≤17mmHg, 56%, 38%; ≤16mmHg, 39%, 26%; ≤15mmHg, 27%, 14%.

COMPLAINT

Allergan stated that only for target IOP ≤15mmHg could the claim 'twice as effective' be considered to be accurate (ratio of effectiveness 1.9), while for ≤16mmHg and ≤17mmHg, it would be more accurate to state 'one and a half times more effective' (ratio of effectiveness 1.5). Even this was not accurate for the remaining IOPs.

Allergan accepted that the statement was '*up to* twice as effective' but considered that the emphasis on 'twice as effective' in both instances made it likely that this was the message which would be conveyed to the reader. The company alleged that this was misleading in breach of Clause 7.2 of the Code.

RESPONSE

Pharmacia & Upjohn did not accept that the claim was misleading. It clearly stated 'Up to twice as effective' and did not purport to imply anything else. Importantly, the ratio of effectiveness as calculated by Allergan was an inappropriate statistical calculation which had been derived by dividing one percentage into another. These were Allergan's own calculations and were a misrepresentation of the data in the original paper by Hedman.

Pharmacia & Upjohn reproduced the table of data from the original paper which showed the odds-ratios for each target IOP for Xalatan and timolol respectively were: ≤20mmHg, 1.9; ≤19mmHg, 1.9; ≤18mmHg, 1.9; ≤17mmHg, 2; ≤16mmHg, 1.8; ≤15mmHg, 2.2.

The data clearly showed for IOP levels of 15 and 17mmHg that the odds-ratio was 2 or above indicating twice as effective or more. For all other IOP levels the odds-ratios were 1.8 or 1.9 and hence very close to 2. It was therefore quite valid to make the statement 'Up to twice as effective' since the statistical data clearly supported this statement.

Pharmacia & Upjohn noted that, according to the author of the paper from which the data were taken, the calculations were based on odds-ratios, and a more

correct statement would be 'over twice as effective as timolol'. The company did not consider, however, from the data presented that the rationale for such a statement would be immediately obvious to its customers, who were not fully conversant with statistical analysis. It therefore decided to go for a lesser claim, still fully supportable, but not, in its opinion, leaving the company open to a claim of exaggeration.

PANEL RULING

The Panel noted the claim above the table of data, 'Up to twice as effective as timolol in reaching target IOPs'. The table stated the percentage of patients who successfully reached specified target IOPs on either Xalatan therapy or timolol therapy. Given the claim above the table the Panel considered that most readers would expect the figures given for Xalatan would be twice those for timolol. For most target IOPs, however, the percentages of patients reaching them in both treatment groups was broadly similar; only for a target IOP of ≤15mmHg was the figure for Xalatan almost twice as large as that for timolol. Reference to the original paper from which the data was taken (Hedman 1997) showed that the claim was based on the calculation of an odds-ratio for each target IOP. The odds-ratios ranged from 1.8 for a target IOP of ≤16mmHg to 2.2 for a target IOP of ≤15mmHg. An odds-ratio of 2.2 signified that the odds of latanoprost-treated patients successfully reaching a target IOP ≤15mmHg was 2.2 times higher than timolol-treated patients.

In the Panel's view the data showed that Xalatan-treated patients were up to twice as likely to achieve target IOPs than timolol-treated patients. There was no explanation however, which would enable to reader to understand that the calculation of odds-ratios formed the statistical basis of the claim 'Up to twice as effective as timolol in reaching target IOPs'. In addition the Panel noted that part of the claim was printed in red ie '…twice as effective…' and considered that most readers would only see that part and so miss the significance of the preceding words 'Up to …'. The Panel considered that the presentation of the data and the highlighting of part of the claim was misleading. A breach of Clause 7.2 was ruled.

Complaint received **30 November 1999**

Case completed **1 February 2000**

CASE AUTH/959/11/99

DIRECTOR/PARAGRAPH 16 v GUERBET

After sales service

During its consideration of Case AUTH/919/8/99 the Panel noted that a letter sent by Guerbet referred to an after sales service in association with a contract for purchasing contrast media. If a contract was awarded the company would offer support as deemed important by the hospital. The Panel considered that this gave the impression that the service was offered as an inducement to prescribe, supply, administer of buy Guerbet's product Xenetix. The Panel decided that the matter should be taken up under Paragraph 16 of the Constitution and Procedure.

The Panel considered that the letter gave the impression that the service items would only be offered if the company was awarded the contract to supply Xenetix and this amounted to an inducement to prescribe, supply, administer or buy the product contrary to the Code. A breach was ruled.

During its consideration of Case AUTH/919/8/99 concerning a letter written by a regional imaging specialist at Guerbet Laboratories Ltd to a chief pharmacy technician at a hospital, the Panel noted that a previous letter sent to the hospital by Guerbet, and headed 'Re:Contract for contrast media', gave details of Xenetix, a non-ionic contrast medium, and referred to an after sales service. The Panel queried whether this service satisfied the requirements of Clause 18.1 of the Code and considered that this matter should be taken up with Guerbet under Paragraph 16 of the Constitution and Procedure.

COMPLAINT

The Panel noted that the initial letter sent to the hospital by Guerbet about Xenetix referred to an after sales service and stated that 'If the contract should be awarded to us [Guerbet] would offer support as deemed important to the department. Areas where we have already been involved include CPD [Continuing Professional Development] training courses, sponsorship of meetings (in-house or regional) medical and non-medical educational funding, medical books etc' The Panel considered that this gave the impression that the after sales service was offered as an inducement to prescribe, supply, administer or buy Xenetix contrary to the provisions of Clause 18.1 of the Code.

RESPONSE

Guerbet provided details of each service item at issue.

CPD training courses: This was where Guerbet facilitated continuous professional development, such as the provision of lectures to radiographers, and put a hospital in touch with outside trainers to enable the outside trainer to enter into a contract with the hospital to provide training as necessary.

Sponsorship of meetings: Guerbet responded to requests for support, such as the funding of an

independent guest speaker, a prize if appropriate or help of a similar nature and type. Most meetings it supported attracted CME credits.

Medical educational funding: Under this category, Guerbet offered support to doctors via education or travel bursaries to enable a doctor to go to a seminar or course. It also funded leading edge independent clinical research in certain circumstances.

Non-medical educational funding: Under this category Guerbet offered lectures to imaging departmental assistants, departmental nurses and radiographers and generally tried to facilitate the learning process for non-medical staff, including helping staff to attend courses.

Medical books: Guerbet supported departments to build their own libraries. Guerbet produced a number of peer reviewed literature and media.

The 'etc' included free literature to support the latest imaging equipment, courses, seminars, lending sets of videos which it retained for training purposes and the funding for procedural and information booklets.

Guerbet stated that it was important to stress that in making offers of this kind, it merely responded to questions, such as in the way it could help departments should it be successful in tendering for a contract. It did not offer any of these examples as an inducement when it tendered for a contract.

Guerbet submitted that the construction of the sentence at issue might possibly be considered to be sloppy, in which case an adverse meaning could be construed in the particular circumstances that caused this letter to be written. Guerbet suggested, however, that the language used did not amount to a clear inducement as provided for in Clause 18.1 of the Code. The list provided in this sentence was an illustration of what it had done in the past for a number of hospitals in response to their requests, within the tender document, to outline any additional educational, departmental or research support it could offer. This did not purport to suggest that all of these services would have been made available in this particular instance.

Such services were provided by other pharmaceutical companies as a matter of course, and Guerbet had to respond to the norms within the industry as well as requests made by hospitals.

PANEL RULING

The Panel noted that Clause 18.1 prohibited the provision of a gift, benefit in kind or a pecuniary advantage to members of the health professions or to administrative staff as a inducement to prescribe, supply, administer or buy any medicine. The supplementary information to Clause 18.1 stated that its provisions did not prevent the provision of medical and educational goods and services which would enhance patient care or benefit the NHS. The provision of such goods or services must not be done in such a way as to be an inducement to prescribe, supply, administer or buy any medicine.

The supplementary information to Clause 18.1 headed 'Package Deals' stated that Clause 18.1 did not prevent the offer of package deals whereby the purchaser of particular medicines received with them other associated benefits, such as apparatus for administration, providing that the transaction as a whole was fair and reasonable.

The Panel considered that the arrangements as described in the letter would not be seen as a package deal as described in the relevant supplementary information.

The Panel noted that a chief pharmacy technician had written to Guerbet inviting it to tender for a contract for contrast media. The letter requested that when Guerbet submitted its quotation it should specify the unit price per vial/bottle including VAT, the pricing structure for a one and two year contract and any delivery charge. There was no request for the company to detail its value added services. Guerbet had responded via the letter in question the penultimate paragraph of which referred to an excellent after sales service and stated that 'If the contract should be awarded to us [Guerbet] would offer support as deemed important to the department'. Examples of support items were then listed. The Panel noted Guerbet's submission about the construction of this sentence. The Panel considered that this paragraph gave the impression that the service items would only be offered if the company was awarded a contract to supply Xenetix and this amounted to an inducement to prescribe, supply, administer or buy the product contrary to the provisions of Clause 18.1 of the Code. The Panel considered that the company could thus not take the benefit of the supplementary information to Clause 18.1 regarding the provision of medical and educational goods and services as the way in which the items had been offered amounted to an inducement. A breach of Clause 18.1 was ruled.

Proceedings commenced 18 October 1999

Case completed 17 January 2000

CASE AUTH/960/12/99

DIRECTOR v PIERRE FABRE

Promotion of Navelbine

An allegation from Rhône-Poulenc Rorer that the promotion of Navelbine (vinorelbine) by Pierre Fabre breached an undertaking and assurance which it had previously given was taken up as a complaint by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings.

Rhône-Poulenc Rorer alleged that at a meeting the Pierre Fabre stand had Navelbine promotional materials available to pick up which were in breach of the undertaking given by Pierre Fabre in Case AUTH/839/2/99. Published papers provided were inconsistent with the licensed indications for Navelbine and a Navelbine Regimens booklet referred to these papers.

The Panel noted that Navelbine was indicated for the treatment of advanced breast cancer stage 3 and 4 relapsing after or refractory to an anthracycline containing regimen. In Case AUTH/839/2/99 three folders promoting Navelbine had each given details of a different study. Included in each patient population were some who had had no prior treatment with an anthracycline but who were nonetheless treated with Navelbine. The data from each study therefore included patients who had not been treated in accordance with the Navelbine summary of product characteristics (SPC). Each folder in effect promoted Navelbine for patients who had not relapsed after, or were refractory to, an anthracycline containing regimen and each had been ruled in breach of the Code in that regard. The booklet 'Navelbine Regimens' (ref PFO 21) had also been at issue then and it had been alleged that this too promoted the use of Navelbine in patients who had not been pre-treated with anthracyclines by advocating its use in those with cardiac risk or in those who refused to have an anthracycline. The Panel had noted, however, that these two patient groups were listed under a heading of 'Problems related to anthracycline use' and considered that on balance that section of the booklet was not in breach of the Code.

In the current case, Pierre Fabre submitted that complete and unabridged scientific papers were only provided by request as a service to clinicians. The Panel noted that the binder which contained the papers available for selection was an integral part of the promotional stand. The Panel considered that whilst such papers could be provided in response to an unsolicited request from a health professional as long as certain requirements were satisfied, the provision of such papers in response to a solicited request at a promotional stand was a promotional activity subject to the Code. The issues were similar to those in Case AUTH/839/2/99. Pierre Fabre had in effect solicited requests for the studies. The studies in question included patients who had not been treated in accordance with the Navelbine SPC. The Panel ruled a breach of the Code in respect of the provision, from a company stand, of the papers reporting those studies. The Panel considered that the provision of the papers was not caught by the undertaking given pursuant to Case AUTH/839/2/99 and ruled no breach in that regard.

The Panel noted that in Case AUTH/839/2/99 the 'Navelbine Regimens' booklet had been ruled not to be in breach of the Code with regard to a statement made on page 5. The allegation in the current case was that, regardless of the no breach ruling, citation of two of the studies at issue elsewhere in the booklet meant that it was caught by the undertaking given in the previous case in respect of the folders. The Panel noted that the Navelbine Regimens booklet gave no details of the two studies, only listing suggested dose and schedules for various combination therapies. The Panel considered that such citation did not promote the use of Navelbine for patients who had not been treated in accordance with the SPC. No breach of the Code in that regard was ruled. The booklet was not caught by the undertaking given in the previous case and so no breach was ruled in that regard either.

Rhône-Poulenc Rorer Limited complained about the promotion of Navelbine (vinorelbine) by Pierre Fabre Ltd. It was alleged that the undertaking given by Pierre Fabre in Case AUTH/839/2/99 had been breached. In accordance with advice previously given by the Appeal Board, the allegation of a breach of undertaking was taken up as a complaint by the Director as the Authority itself was responsible for ensuring compliance with undertakings.

COMPLAINT

Rhône-Poulenc Rorer stated that on 16 November 1999, one of its area managers attended the Leeds Cancer Centre Breast Services educational meeting. The Pierre Fabre stand had promotional materials available for delegates to pick up and the area manager collected five items:

1 Fumoleau *et al* (1993) published paper

2 Spielmann *et al* (1994) published paper

3 Dieras *et al* (1996) published paper

4 Blajman *et al* (1999) published paper

5 Navelbine Regimens (PFO 21)

Rhône-Poulenc Rorer stated that items 1, 2 and 3 were the reference papers upon which the promotional materials found in breach of Clause 3.2 in Case AUTH/839/2/99 were based. Item 4 was another paper that sought to promote outside of the licensed indication for Navelbine. Only 11 out of the 85 patients assessed on the vinorelbine/doxorubicin regime were known to have been treated with anthracyclines (13%). In relation to item 5, according to the case report for Case AUTH/839/2/99 '… Pierre Fabre had already reviewed all its promotional material as a consequence of previous correspondence. The booklet (PFO 21) had been replaced with an updated version, (PFO 36).' Although not found in breach, there were statements in the text which referred to Spielmann *et al* and Dieras *et al* (items 2 and 3) which were found in breach.

Rhône-Poulenc Rorer alleged that the continued use of such materials discredited and reduced confidence in the pharmaceutical industry.

RESPONSE

Pierre Fabre noted that the previous case, Case AUTH/839/2/99, related to promotional material printed and produced by the company in 1998. The code numbers were PFO 21, 22, 23 and 24.

Pierre Fabre stated that the Panel ruling on the regimens booklet, PFO 21, was of no breach of the Code. No action by Pierre Fabre was therefore required on this matter, which it believed to be closed. There was no justification for a further complaint about this item and therefore no case to answer. Other promotional materials in Case AUTH/839/2/99 were coded PFO 22, 23 and 24. These items had not been in use since November 1998 and were not the subject of this complaint either. As it had not used any promotional material that had been ruled in breach of the Code, there was no case to answer in this matter.

Pierre Fabre stated that the use of cytotoxic chemotherapy was amongst the most rigorously controlled areas of prescribing in the UK. Many believed that this was a contributing factor to the relatively poor outcome for patients with cancer in the UK. For any cytotoxic medicine to be made available for the treatment of NHS patients, oncologists were obliged to conduct an extensive scientific evaluation of the proposed intervention for presentation to the purchasers. The advantages of the medicine must be balanced with the unpleasant side effects and associated morbidity. This analysis was achieved with a review of the published literature. Whenever two or more medicines were used in combination, as they frequently were, published papers were the only source of clinical data on toxicity, dose and schedule. Oncologists were recognised for their skill in understanding and evaluating these data from published clinical trials. NHS use of modern chemotherapy medicines, where permitted, was strictly according to protocols agreed with the purchasers. Any proposed use in unlicensed indications would not pass such a scientific review and would certainly not be approved by purchasers.

Pierre Fabre stated that the four clinical papers available from its stand had been published in journals which were highly regarded by oncologists and were already available in every cancer hospital in the UK. Complete and unabridged scientific papers were only provided by request as a service to clinicians and were intended to facilitate the scientific debate in cancer care and were not used as promotional items.

Pierre Fabre submitted that this was a reasonable and responsible approach in a complex and highly specialised therapy area. Provision of peer-reviewed and published clinical experience to facilitate scientific review was a credit to the industry and enhanced confidence in it. There was no case to answer in this matter.

In response to a request for further information, Pierre Fabre stated that clinical papers were taken to meetings by its representatives. They were kept in a clear plastic binder that was clearly marked 'Available by Request'. The binder was visible on the display but individual papers were obscured. A form was displayed prominently so that clinicians were able to request specific clinical papers. A small number of extra copies of papers were carried as they were frequently requested with a degree of urgency. These were not routinely displayed but would be accessible to a determined individual.

The Pierre Fabre exhibition stand included a number of support items, body surface area calculators, pens, notepaper, administration and TNM (Tumour, Node, Metastasis - used in staging patients) posters and slides. Pierre Fabre stated that the only 'promotional' brochure used was the regimens booklet.

The meeting was attended by members of the breast cancer teams, oncologists, surgeons and breast care nurses.

Pierre Fabre stated that its handling of clinical papers was cautious and measured. It was intended to facilitate the scientific evaluation of combination treatments.

PANEL RULING

The Panel noted that Navelbine was indicated for the treatment of advanced breast cancer stage 3 and 4 relapsing after or refractory to an anthracycline containing regimen. In Case AUTH/839/2/99 three folders promoting Navelbine had each given details of a different study (Fumoleau *et al*, Spielmann *et al* and Dieras *et al* respectively). Included in each patient population were some who had had no prior treatment with an anthracycline but who were nonetheless treated with Navelbine. The data from each study therefore included patients who had not been treated in accordance with the Navelbine summary of product characteristics (SPC). Each folder in effect promoted Navelbine for patients who had not relapsed after, or were refractory to, an anthracycline containing regimen. Each folder had been ruled in breach of Clause 3.2 of the Code in that regard.

The booklet 'Navelbine Regimens' (ref PFO 21) had also been at issue in Case AUTH/839/2/99. It was alleged that this too promoted the use of Navelbine in patients who had not been pre-treated with anthracyclines by advocating its use in those with cardiac risk or in those who refused to have an anthracycline. The Panel had noted, however, that these two patient groups were listed under a heading of 'Problems related to anthracycline use' and considered that on balance that section of the booklet was not in breach of Clause 3.2 of the Code.

Turning to the case now before it the Panel noted that the papers by Fumoleau *et al*, Spielmann *et al* and Dieras *et al*, upon which the three folders found in breach of Clause 3.2 in Case AUTH/839/2/99 were based, had been available from the Pierre Fabre stand. A fourth paper, Blajman *et al* (1999), similarly included some patients who were treated with Navelbine despite having had no prior treatment with an anthracycline. The Panel noted Pierre Fabre's submission that the papers were kept in a clear plastic

binder clearly marked 'Available by Request' and that individual papers were obscured. A form which was prominently displayed listed available items. The last item listed was clinical papers, followed by 'please specify' adjacent to which there was a box for readers to identify the required paper. There was provision for the name, hospital address and telephone number of the health professional.

The Panel noted that this was a complex therapy area. Pierre Fabre had submitted that complete and unabridged scientific papers were only provided by request as a service to clinicians. The Panel noted that the binder was an integral part of the promotional stand and contained the papers available for selection. The Panel considered that whilst such papers could be provided in response to an unsolicited request from a health professional as long as the requirements of Clause 1.2 were satisfied, the provision of such papers in response to a solicited request at a promotional stand was a promotional activity subject to the Code.

The Panel noted that the issues were similar to those in Case AUTH/839/2/99. The Panel noted that Pierre Fabre had in effect solicited requests for the studies. They were being used for a promotional purpose. This therefore meant that the studies had to be in accordance with the Code. The studies in question included patients who had not been treated in accordance with the Navelbine SPC. The Panel ruled a breach of Clause 3.2 of the Code in respect of the provision, from a company stand, of the papers reporting those studies.

The Panel considered that the provision of the papers was not caught by the undertaking given pursuant to Case AUTH/839/2/99 and ruled no breach of Clauses 21 and 2.

The Panel noted that in Case AUTH/839/2/99, the 'Navelbine Regimens' booklet had been ruled not to be in breach of the Code with regard to a statement made on page 5. The allegation in the current case was that, regardless of the no breach ruling, citation of the studies by Spielmann *et al* and Dieras *et al* elsewhere in the booklet meant that it was caught by the undertaking given in the previous case in respect of the folders.

The Panel noted that two of the folders at issue in the previous case had given details of inclusion/eligibility criteria, patient characteristics and response as reported by Spielmann *et al* and Dieras *et al*. Data had been presented from the whole of each study population to include those patients who had received Navelbine despite having had no previous anthracycline therapy. The Navelbine Regimens booklet, however, gave no details of the two studies only listing suggested dose and schedules for various combination therapies. Spielmann *et al* was cited in support of the combined use of Navelbine and doxorubicin and Dieras *et al* in support of the combination of Navelbine with 5-FU. The Panel considered that such citation did not promote the use of Navelbine for patients who had not been treated in accordance with the SPC. No breach of Clause 3.2 was ruled. The booklet was not caught by the undertaking given in the previous case and so no breach of Clauses 21 and 2 was ruled.

Complaint received **3 December 1999**

Case completed **25 February 2000**

CASE AUTH/961/12/99

PHARMACEUTICAL ADVISER v ASTRAZENECA

Sponsorship of evidence based workshop

A health authority pharmaceutical adviser complained about notice of an evidence based workshop on the use of atypical antipsychotics which failed to disclose that it had been sponsored by AstraZeneca.

The Panel noted that AstraZeneca accepted that this had been an error on its part. The company had not intended to mislead and its involvement would have become known as the contact person was an AstraZeneca representative. A breach of the Code was ruled.

COMPLAINT

A health authority pharmaceutical adviser complained about notice of an evidence based workshop on the use of atypical antipsychotics which failed to disclose the sponsoring body, giving only the name and telephone number of the person with whom places should be reserved. On enquiring as to the availability of places and the cost, the complainant was informed that the workshop was free and was funded by AstraZeneca. A breach of Clause 9.9 of the Code was alleged.

RESPONSE

AstraZeneca noted that Clause 9.9 of the Code stated 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. AstraZeneca accepted that the poster did not indicate that the meeting was sponsored by AstraZeneca and it apologised for the unfortunate error.

This was a genuine error on AstraZeneca's part and there was no intention to mislead as to the nature of the meeting. AstraZeneca's involvement in the meeting would inevitably have become obvious to respondents as the contact person was the local AstraZeneca representative.

AstraZeneca had taken immediate action to ensure that no other posters of a similar nature were in use and it had reviewed its staff training procedures to ensure that an error such as this would not recur.

PANEL RULING

The Panel noted that AstraZeneca had accepted that it was in breach of Clause 9.9 of the Code as sponsorship had not been declared. A breach of that clause was ruled.

Complaint received **16 December 1999**

Case completed **1 February 2000**

CASE AUTH/963/12/99

UNIVERSITY CLINICAL READER v RECKITT & COLMAN

Buccastem mailing

A university clinical reader complained about a mailing for Buccastem (prochlorperazine by the buccal route) issued by Reckitt & Colman. The front cover claimed 'Effective, long lasting relief from nausea and vomiting … whatever the cause' which, in the complainant's view, was flagrant hyperbole and clearly misleading.

The Panel noted from the summary of product characteristics that Buccastem was licensed for the symptomatic treatment of vertigo due to Ménière's Disease, labyrinthitis and other causes, for nausea and vomiting from whatever cause and for the treatment of migraine. With regard to the claim in question the Panel therefore considered that 'Effective … relief from nausea and vomiting … whatever the cause' was covered by the licence. The claim that such relief was long lasting would, however, need to be supportable. The Panel reviewed the papers cited in substantiation of the claim but on the basis of these considered that the claim for long lasting relief could only be made in respect of nausea and vomiting resulting from vertiginous disorders and it was thus misleading. A breach of the Code was ruled.

A university clinical reader complained about a mailing for Buccastem (prochlorperazine by the buccal route) which he had received from Reckitt & Colman Products Limited. The letter of complaint had been copied to Reckitt & Colman. The front cover of the mailing stated 'Effective, long lasting relief from nausea and vomiting … whatever the cause'.

COMPLAINT

The complainant said that it was claimed that Buccastem provided effective, long lasting relief whatever the cause. In the complainant's view this was clearly an example of flagrant hyperbole and was clearly misleading.

RESPONSE

Reckitt & Colman stated that it did not consider that the material was misleading. The claim had to be put into context, namely, the leaflet was directed towards comparing Buccastem which was delivered by the buccal route with oral prochlorperazine. The claim for effective and long lasting relief could be substantiated with data by Bond (1998) and Hesell *et al* (1989).

Reckitt & Colman pointed out the claim for relief from nausea and vomiting whatever the cause was in accordance with the terms of the marketing authorization for the product and consistent with the particulars in the summary of product characteristics (SPC). This indication for the product was allowed by the Medicines Control Agency after consideration of information generally known concerning products of this nature and confidential data submitted by Reckitt & Colman.

Reckitt & Colman stated that until it received the copy of the letter sent to the Authority it was unaware that the complainant objected to the promotion. Immediately on receipt of the letter it took action to contact the complainant to address his concerns but through an internal misunderstanding the proposed letter was never sent. While Reckitt & Colman did not consider that the advertisement was misleading it of course valued the comments of persons such as the complainant and on receipt of his copy letter took the decision not to repeat the promotion in the form complained of.

PANEL RULING

The Panel noted from the SPC that Buccastem was licensed for symptomatic treatment of vertigo due to Ménière's Disease, labyrinthitis and other causes, for nausea and vomiting from whatever cause and for the treatment of migraine. With regard to the claim in question the Panel therefore considered that 'Effective … relief from nausea and vomiting … whatever the cause' was covered by the licence. However the claim that such relief was long lasting would need to be supportable.

The Panel noted the references cited in substantiation of the claim. The study by Bond (1998) had compared oral and buccal prochlorperazine in the treatment of dizziness associated with nausea and/or vomiting in patients suffering from vertiginous disorders. Results showed that the buccal preparation achieved a faster onset of effect compared with oral prochlorperazine and was significantly better in reducing frequency of nausea and severity of vomiting at 24-36 hours. In the Panel's view the study supported the claim 'long-lasting relief' but only for nausea and vomiting resulting from vertiginous disorders, not from all causes. The paper by Hessell *et al* (1989) was a report on a series of pharmacokinetic studies in non-patient volunteers.

On the basis of the papers put before it the Panel considered that the claim for long lasting relief in question over-stated the data and was thus misleading. A breach of Clause 7.2 was ruled.

Complaint received **21 December 1999**

Case completed **7 February 2000**

CASE AUTH/964/12/99

ASTRAZENECA v WYETH

Promotion of Zoton and failure to comply with undertaking

AstraZeneca complained about comparisons of its product Losec (omeprazole) with Zoton (lansoprazole) contained in a cost calculation wheel and a detail aid produced by Wyeth.

The cost calculation wheel could be used to calculate the monthly and annual costs associated with prescribing the most commonly used doses of Zoton and omeprazole in reflux maintenance (15mg and 20mg respectively) for stated numbers of patients. AstraZeneca stated that the calculation was based on an assumption of equal efficacy and alleged that it was misleading to claim equivalence and that Zoton 15mg and omeprazole 20mg were interchangeable. The selection of these doses excluded the substantial subset of patients who were maintained on Zoton 30mg and omeprazole 10mg. AstraZeneca pointed out that the direct comparison of Zoton 15mg vs omeprazole 20mg had been ruled misleading in two previous cases.

The Panel considered that the cost calculator gave the impression that the doses of Zoton 15mg and omeprazole 20mg were therapeutically equivalent; it was not unreasonable for some readers to assume that in reflux maintenance it was a simple choice between the two. There was data to show that omeprazole 20mg was significantly more effective than Zoton 15mg. Other doses of the two medicines could be used. The Panel noted that in the maintenance of reflux 59% of Zoton-treated patients were prescribed 15mg and 74% of omeprazole-treated patients were prescribed 20mg. The cost calculator thus accounted for different percentages of patients. The Panel ruled a breach as the cost calculator did not provide a fair comparison.

The Panel noted that AstraZeneca had referred to previous rulings of breaches of the Code. The Panel noted that although the material at issue in this case was not the same as the material previously at issue it was nonetheless sufficiently similar such that it represented a failure to comply with the undertakings. A breach of the Code was ruled in this regard.

A page in the detail aid headed 'Reflux oesophagitis maintenance therapy' used data from studies with similar endoscopic endpoints and listed the range of endoscopic remission rates at 12 months in reflux oesophagitis for Zoton 15mg and 30mg and omeprazole 10mg and 20mg. Additionally the results for Zoton 15mg were depicted in a graph; AstraZeneca alleged that this was not appropriate as the five separate studies cited had different inclusion criteria, oesophagitis grading systems and endpoints. Further AstraZeneca alleged that an asterisk immediately beneath the graph which stated 'Omeprazole 20mg vs lansoprazole 15mg: <0.001' did not reflect the balance of the evidence. AstraZeneca stated that the presentation of data in this way had previously been ruled in breach of the Code.

The Panel noted that in the previous case the claim 'Zoton 15mg – comparable 12 month remission rates to omeprazole 20mg' had been ruled in breach as there was data to show a statistically significant difference between Zoton 15mg and omeprazole 20mg. The use of non-comparative data to support the claim was ruled to be misleading.

The Panel considered that the circumstances in this case were different to the previous case in that there was no clear claim for comparability. However, listing the remission rate ranges invited the reader to make direct comparisons and so gain the impression that lansoprazole 15mg and 30mg and omeprazole 20mg were all comparable. This was not so. The Panel considered that the presentation of the remission rates was misleading and a breach of the Code was ruled. The Panel considered that the material was sufficiently different from that previously ruled in breach of the Code such that it did not represent a failure to comply with an undertaking. No breach of the Code was ruled in that regard.

The studies cited in support of lansoprazole 15mg had varying inclusion criteria but similar healing criteria. In the Panel's view it was not unacceptable to state that they had similar endoscopic endpoints. No breach of the Code was ruled.

An allegation with regard to a cost comparison of maintenance therapy in the detail aid was covered by the rulings made in relation to the cost calculator.

AstraZeneca complained about the promotion of Zoton (lansoprazole) by Wyeth. The materials consisted of a proton pump inhibitor (PPI) cost calculator (ref ZZOT1084/0799) and a detail aid 'Upper GI Therapy Review' (ref ZZOT1091/1199). AstraZeneca marketed Losec (omeprazole).

1 PPI Cost Calculator

This item was a cost calculation wheel which stated that it compared the differences in cost between the most commonly prescribed doses of Zoton (15mg; £14.21/28 days) and omeprazole (20mg; £28.56/28 days) in reflux maintenance. The cost calculator could be used to calculate the monthly and annual costs and savings associated with prescribing Zoton 15mg, as opposed to omeprazole 20mg, for 10, 50, 100, 200, 500, 750 or 1000 patients. The item also included the basic NHS prices for 28 days of Zoton 30mg (£28.15) and omeprazole 10mg (£18.91). The item was used as a representatives' leavepiece.

COMPLAINT

AstraZeneca stated that the calculation was based on an assumption of equal efficacy of omeprazole (Losec) 20mg and lansoprazole (Zoton) 15mg in reflux maintenance. The selection of these doses was based on the most commonly prescribed doses for each product and was clearly stated on the piece. This cost calculator, therefore, actively excluded the substantial subset of patients who were maintained on omeprazole 10mg and lansoprazole 30mg for acid reflux disease. Indeed, according to the figures cited

in Wyeth's booklet 'Upper GI Therapy Review' (page 19) the percentage of patients maintained on these doses were 26% and 41% respectively.

In the only scientifically valid, direct comparison of lansoprazole 15mg vs omeprazole 20mg undertaken in the maintenance of gastro-oesophageal reflux disease (GORD), lansoprazole 15mg was found to be significantly less effective than omeprazole 20mg over one year in a large trial of 906 patients (Baldi *et al* 1996). This finding was further supported by work by Carling *et al* (1998) who reported that lansoprazole 30mg had equivalent efficacy to omeprazole 20mg in the maintenance of healing over a one-year period. These data supported the conclusion that omeprazole 20mg was significantly more effective than lansoprazole 15mg in GORD maintenance. Moreover, the licensed daily doses in the maintenance of GORD were 15mg and 30mg for lansoprazole and 10mg and 20mg for omeprazole.

On the basis of the above, it was misleading to claim that lansoprazole 15mg was equivalent to omeprazole 20mg in GORD and that the two were interchangeable, as implied in the PPI cost calculator. Indeed, in recognition of the point made above, in a previous case, Case AUTH/676/2/98, Wyeth was ruled in breach of Clause 7.2 for comparing the price of the lowest maintenance dose of lansoprazole (15mg) with the price of the highest maintenance dose of omeprazole (20mg) in GORD. Similarly, in a later case, Case AUTH/745/7/98, rulings of breaches of Clauses 2 and 7.2 were made in that it was unacceptable to present lansoprazole 15mg as equivalent to omeprazole 20mg for remission rates. Thus, as the direct comparison of lansoprazole 15mg vs omeprazole 20mg had been ruled as misleading and in breach of Clause 7.2 twice within the last 18 months, AstraZeneca alleged the PPI cost calculator was in breach of Clause 7.2.

RESPONSE

Wyeth stated that as the current debate amongst clinicians in respect of the choice of long-term PPI therapy for reflux maintenance revolved around choosing between Zoton 15mg and omeprazole 20mg, it was obviously appropriate to cite a comparison based upon the two most commonly prescribed products used in this indication. This debate was taking place in an NHS where cost containment was becoming an increasing priority and consequently the cost-effectiveness of treatments was of critical importance. Hence the price difference between Zoton 15mg (£14.21) and omeprazole 20mg (£28.56) represented a substantial saving to the NHS.

With regard to the allegation that the current complaint represented a breach of an undertaking given in a previous case, Wyeth stated that it considered that both the PPI cost calculator and the 'Reflux oesophagitis maintenance therapy' page in the detail aid (see point 2a below) were significantly different in context compared to the material previously ruled in breach.

Wyeth stated that AstraZeneca's two basic assumptions that the PPI cost calculator related to clinical equivalence and implied interchangeability were incorrect in that the item clearly depicted the comparison as being based upon the two most commonly prescribed doses of Zoton and omeprazole in initiating reflux maintenance.

Also, in the clearly stated context of the comparison being based upon the two most commonly prescribed doses of Zoton and omeprazole, namely 15mg and 20mg respectively, it would seem inappropriate for AstraZeneca to assert that comparisons with both omeprazole 10mg and lansoprazole 30mg should be included. In contrast, Wyeth submitted that the inclusion of the basic NHS prices for the four comparative strengths, as a reflection of all the licensed reflux maintenance doses for the products, was the correct approach.

Similarly, Wyeth did not understand the relevance of AstraZeneca referring to clinical head-to-head comparisons as the comparison was based upon the most commonly prescribed doses of Zoton and omeprazole in reflux maintenance.

Consequently, Wyeth did not consider that it was in breach of Clause 7.2.

PANEL RULING

The Panel considered that, contrary to Wyeth's submission, the cost calculator gave the impression that the doses of Zoton 15mg and omeprazole 20mg were therapeutically equivalent. In the Panel's view it was not unreasonable for some readers to assume that in reflux maintenance it was a simple choice between prescribing Zoton 15mg or omeprazole 20mg. The Baldi *et al* (1996) data had shown that omeprazole 20mg was significantly more effective than lansoprazole 15mg. The Zoton summary of product characteristics (SPC) stated that for long-term management of GORD a maintenance dose of 15mg or 30mg once daily could be used depending on patient response. The Losec SPC stated that in GORD the usual dose was 20mg once daily. Losec 40mg was used in patients with GORD refractory to other therapy. Healing usually occurred within eight weeks. Patients could be continued at a dose of 20mg once daily. For the long-term management of acid reflux disease, Losec 10mg daily was recommended, increasing to 20mg if symptoms returned.

The Panel noted that in the maintenance of reflux 74% of patients were prescribed omeprazole 20mg and 26% received 10mg. For Zoton, 59% of patients were prescribed 15mg and 41% received 30mg. The cost calculator, in considering only the costs of omeprazole 20mg and Zoton 15mg, therefore accounted for 74% and 59% of patients respectively.

The Panel considered that cost calculator did not provide a fair comparison. Zoton 15mg and omeprazole 20mg were not the only doses of each medicine which could be used in reflux maintenance, the impression given was that they were therapeutically equivalent and although they were the most commonly prescribed doses of each medicine, they accounted for different percentages of patients. A breach of Clause 7.2 was ruled.

The Panel noted that AstraZeneca had referred to previous rulings of breaches of the Code in Cases

AUTH/676/2/98 and AUTH/745/7/98. The Panel noted that the material at issue in this case was not the same as the material at issue in the previous two cases. The Panel considered that nonetheless the material was sufficiently similar such that it represented a failure to comply with the undertakings given in the previous cases. The Panel therefore ruled a breach of Clause 21 of the Code. The Panel considered that in the circumstances there was no breach of Clauses 2 and 9.1 of the Code in this regard.

2 Upper GI Therapy Review

This item was a 33 page detail aid. It was sub-headed 'A case for lansoprazole. Evidence based medicine'.

a Page 18 headed 'Reflux oesophagitis maintenance therapy'

The page gave details of endoscopic remission rates at 12 months in reflux oesophagitis, using data drawn from studies with similar endoscopic endpoints, as follows: lansoprazole 15mg 69-87%, omeprazole 10mg 50-60%, omeprazole 20mg 65-90% and lansoprazole 30mg 80-90%. The results for lansoprazole 15mg were shown in a graph which gave the results from five studies, Baldi *et al* (1996), Poynard *et al* (1995), Robinson *et al* (1996), Gough *et al* (1996) and Hatlebakk and Berstad (1997). The reference to Baldi included an asterisk and the explanation 'omeprazole 20mg vs lansoprazole 15mg: <0.001' appeared immediately below the graph. It was stated that the data came from studies with similar endoscopic endpoints.

COMPLAINT

AstraZeneca alleged that the basis for the comparison as depicted in the graph was not appropriate, namely that the data were drawn from five separate studies with similar, but not equivalent, endoscopic endpoints.

In uncontrolled comparisons of studies of GORD maintenance there was great potential for bias:

i Bias due to comparison of differing patient populations. The rates of alcohol use, obesity and other factors could affect reflux and thus GORD leading to unfair comparisons of data.

ii Bias due to differing grades of oesophagitis at entry to the study. If comparisons were made using differing severity levels of oesophagitis at entry before healing, the implication was that these patients had differing disease processes (pathologically and possible aetiologically). As such, they were not comparable populations.

iii A comparison of 'healing rates' between trials could be misleading in one important respect. In the different trials not only were different grading systems used for oesophagitis but also the criteria for healing were different. This meant that in some trials complete healing of normal mucosa was used as an endpoint, and in others grade 1 healing usually patchy erythema and eradicates were used. The use of the end point 'normal mucosa' was a more stringent test than 'patchy, non-confluent erythema with or without exudate' and more people could, therefore, be expected to fail this test than when less strict end points were used.

Thus, amalgamated data comparisons used in GORD suffered from these large potential biases. The differences between the studies cited were as follows:

Study	*Inclusion Criteria*	*Healing Criteria*
Baldi (1996)	Grade l - lV	Grade 0 Grade ≥ 1 relapse
Poynard (1995)	Grade ll - lV	
Robinson (1996)	Grade ll - lV [Modified Savary Miller]	Grade 0 or 1
Gough (1996)	Grade ll - lll	Grade ≥ 1 relapse
Hatlebakk (1997)	Grades l & ll (Berstad)	Grade ≥ 1 relapse

In summary, the studies cited had different inclusion criteria based on different grades of oesophagitis on entry, different oesophagitis grading systems and there was confusion as to the endpoints used for healing in the studies. The endpoint remission rates were, therefore, non-comparable as they involved different levels of healing or oesophagitis measured on different criteria.

Further, AstraZeneca alleged that it was unbalanced to place undue emphasis, by the use of an asterisk immediately beneath the graph, to highlight a comparison and a significance level versus omeprazole 20mg, but that did not reflect the balance of evidence as detailed below.

As stated previously, there were two studies (Baldi (1996), Carling (1998)) which directly compared omeprazole 20mg and lansoprazole 30mg in reflux oesophagitis long-term maintenance. Carling (1998) compared lansoprazole 30mg with omeprazole 20mg in maintenance of healing over a one year period. Omeprazole 20mg and lansoprazole 30mg were of equivalent efficacy in the maintenance of reflux oesophagitis. The interpretation of data from Baldi (1996) related to two separate representations of data from the study. The abstract of this study, which did not contain any statistical analysis, stated that the doses compared, lansoprazole 15mg, lansoprazole 30mg and omeprazole 20mg, were not significantly different over a one year period. The Baldi poster (1996) contained the statistical analysis of the data. It described the primary endpoint as rates of endoscopic remission after 12 months of treatment. The analysis of this primary endpoint showed statistically significant differences in rates of patients in remission on the all patients treated analysis.

- Omeprazole 20mg (90%) vs lansoprazole 15mg (76%) $p<0.01$
- Omeprazole 20mg (90%) vs lansoprazole 30mg (91%) $p<0.989$
- Lansoprazole 15mg (76%) vs lansoprazole 30mg (91%)$p<0.001$

In the light of these findings and considering the amalgamated data comparison which suffered from a

number of biases, the balance of evidence demonstrated lansoprazole 15mg to be significantly less effective in maintenance of GORD than either omeprazole 20mg or lansoprazole 30mg.

AstraZeneca stated that the presentation of the data in this way had previously been ruled in breach (Case AUTH/745/7/98) in that it was unacceptable to present lansoprazole 15mg as equivalent to omeprazole 20mg for remission. The premise of this ruling was that it was unacceptable to make an equivalence claim for remission rates over 12 months based on a comparison of amalgamated non-comparative trial data.

Although modified in this piece, the continued use of the non-comparative amalgamated data and its juxtaposition to remission rate ranges quoted for omeprazole 10mg, 20mg and 30mg invited a misleading comparison of non-comparative data.

A breach of Clause 7.2 of the Code was alleged.

RESPONSE

Wyeth stated that the purpose of the page was to give the clinician a realistic impression of the performance which could be expected from lansoprazole 15mg as reflux maintenance therapy. Wyeth submitted that the page appropriately showed lansoprazole 15mg in its own right as effective low-dose reflux maintenance therapy. The depiction reflected the full range of data available for this well-established endpoint, as well as including reference to the one comparative study, and consequently reflected the balance of evidence.

In Wyeth's view it was correct in the stated context to reflect all four dosages of lansoprazole and omeprazole licensed for reflux maintenance. Therefore, it had included the ranges of 12 month reflux endoscopic remission rates for the other three comparators in their own separate context, with Zoton 15mg being depicted in a clearly distinct setting. There was no attempt to show equivalence.

In summary, Wyeth stated that it clearly and appropriately depicted Zoton 15mg in its own right and attempted to show the ranges of data available for the other licensed doses and therefore did not consider the page to be misleading and in breach of Clause 7.2.

PANEL RULING

The Panel noted that the page in question gave all the results for the remission rates for lansoprazole 15mg. It noted AstraZeneca's allegation that the studies were different and the endpoint remission rates were not comparable.

The Panel noted that in the previous case, Case AUTH/745/7/98, a claim 'Zoton 15mg – comparable 12 month remission rates to omeprazole 20mg' had been ruled in breach as the Baldi *et al* data had shown a statistically significant difference between Zoton 15mg and omeprazole 20mg. The use of non-comparative data to support the claim was ruled to be misleading.

The Panel considered that the circumstances in this case were different to the previous case in that there was no clear claim for comparability. However, listing the remission rate ranges invited the reader to make direct comparisons and so gain the impression that lansoprazole 15mg and 30mg and omeprazole 20mg were all comparable. This was not so. The comparative study by Baldi *et al* showed an advantage for omeprazole 20mg over Zoton 15mg and an advantage for Zoton 30mg over Zoton 15mg. The Panel considered that the presentation of the remission rates was misleading and a breach of Clause 7.2 was ruled.

In its response to point 1 above Wyeth had stated that with regard to the allegation of a breach of undertaking the page in the detail aid now at issue was sufficiently different in context compared to the previous material. The Panel considered that the material was sufficiently different from that previously ruled in breach of the Code such that it did not represent a failure to comply with an undertaking. No breach of Clauses 21, 2 and 9.1 was ruled.

The five studies cited in support of lansoprazole 15mg had varying inclusion criteria but similar healing criteria. In the Panel's view it was not unacceptable to state that the studies had similar endoscopic endpoints. No breach of Clause 7.2 of the Code was ruled.

b Page 19 headed 'Potential cost savings'

The page was headed 'Potential cost savings'. The lower part of the page was headed 'Costs of successfully maintaining 100 patients for one year' with a sub-heading 'most commonly prescribed maintenance doses' and included a bar chart which compared the cost of lansoprazole 15mg/28 days, £14.21, giving an annual figure of £18,473 and the cost of omeprazole 20mg/28 days, £28.56, giving an annual figure of £37,128. Beneath the bar chart similar details for omeprazole 10mg and lansoprazole 30mg were given.

COMPLAINT

AstraZeneca alleged that the direct comparison of the relative costs of lansoprazole 15mg and omeprazole 20mg, in the absence of other dosages of protein pump inhibitors, was misleading as it inferred that the two doses were equivalent. On the basis of the available evidence, as opposed to usage data, a cost comparison of lansoprazole 15mg vs omeprazole 10mg or lansoprazole 30mg vs omeprazole 20mg would be more appropriate.

For the reasons cited previously and above, AstraZeneca alleged this was misleading in breach of Clause 7.2.

RESPONSE

Wyeth stated that it was clearly evident and within the context of the whole page, that the bar chart comparisons were based upon the two most commonly prescribed doses of Zoton and omeprazole in reflux maintenance and also that the less commonly prescribed doses were stated immediately below the bar chart in order to reflect the whole range of licensed doses.

Consequently, AstraZeneca was incorrect in claiming that the depiction was based upon efficacy data, not least as, contrary to AstraZeneca's observation, the other dosages were also stated.

Moreover, it was disparaging for AstraZeneca to suggest which cost comparisons would be more appropriate, as based upon the available evidence AstraZeneca had failed to include the Bardhan and Crouch data which showed that lansoprazole 15mg was significantly better than omeprazole 10mg in relation to 12 month reflux remission rates (75% v 60%, p=0.009).

Consequently, Wyeth submitted that the overall page was clearly based upon usage data and that the comparisons were both clearly and appropriately depicted and therefore not in breach of Clause 7.2.

In conclusion, it was disingenuous of AstraZeneca to suggest that Wyeth had not complied with previous rulings.

PANEL RULING

The Panel considered that its rulings in point 1 above also applied here. Breaches of Clauses 7.2 and 21 of the Code were ruled. No breach of Clauses 2 and 9.1 was ruled.

Complaint received **23 December 1999**

Case completed **13 March 2000**

CASE AUTH/965/12/99 ***NO BREACH OF THE CODE***

BOEHRINGER INGELHEIM v MERCK SHARP & DOHME

Promotion of Vioxx

Boehringer Ingelheim complained about a comparison that was made between its product, meloxicam, and diclofenac in a booklet promoting Vioxx (rofecoxib) issued by Merck Sharp & Dohme. On a double page spread headed 'Vioxx versus conventional NSAIDs' two graphs appeared which depicted the mean percentage inhibition of COX-1/COX-2 respectively of *inter alia* meloxicam and diclofenac. The graphs suggested that meloxicam had a more potent effect on COX-1 activity than diclofenac which Boehringer Ingelheim alleged discredited the positioning of meloxicam as a selective COX-2 inhibitor. The data was from a healthy volunteer study by Schwartz in which COX-1 and COX-2 activity had been measured using a whole blood *ex vivo* assay. Boehringer Ingelheim pointed out that Merck Sharp & Dohme had failed to take into account the overall scientific evidence. Reference was made to results obtained using an alternative assay method to measure COX-1/COX-2 activity which showed that meloxicam was more COX-2 selective than diclofenac.

The Panel noted that there was some debate about how COX-1/COX-2 selectivity ought to be measured. An international consensus meeting reported in 1999 recommended that the human whole blood assay be used to determine COX specificity. The relevant pages in the detail aid stated that the COX-1/COX-2 activity was measured using whole blood *ex vivo* assay in healthy volunteers. The relative positioning of meloxicam and diclofenac fairly reflected the results of Schwartz *et al*. The Panel noted that studies had indicated differences between meloxicam and diclofenac. Such differences depended on the assay method. The Panel considered that on balance the data presented were not inconsistent with the overall scientific evidence. The Panel did not accept that the graphs were misleading. No breach of the Code was ruled.

Boehringer Ingelheim Limited complained about an eight page promotional booklet (ref 05-00 VOX.99.GB.65179.B.1m.QO.599) for Vioxx (rofecoxib) produced by Merck Sharp & Dohme Limited. The booklet was referred to as an 'obstacle handler'. Pages two and three of the item headed 'Vioxx versus conventional NSAIDs' discussed the whole blood *ex vivo* assay method in healthy volunteers and featured two graphs which respectively compared the mean percentage inhibition of COX-1 and COX-2 of placebo, Vioxx (12.5mg and 25mg), meloxicam, diclofenac, ibuprofen and naproxen. Each graph and the assay method statement were referenced to data on file. Boehringer Ingelheim produced meloxicam.

COMPLAINT

Boehringer Ingelheim stated that its concern was the misrepresentation of the cyclo-oxygenase (COX) inhibition/selectivity of meloxicam with particular reference to comparison with diclofenac.

Boehringer Ingelheim referred to its letter to Merck Sharp & Dohme, a copy of which was provided, in which it highlighted its concern that these data were being used to misrepresent meloxicam's positioning with respect to diclofenac and hence discredit the positioning of meloxicam as a selective COX-2 inhibitor. The graphs, as presented in the promotional item, suggested that meloxicam had a more potent effect on COX-1 activity than diclofenac.

Boehringer Ingelheim pointed out that meloxicam was a COX-2 selective inhibitor with a selectivity towards COX-2 of 10 fold in the whole blood assay (WBA) as reported in a Merck Sharp & Dohme sponsored 'Highlights' booklet of the William Harvey Research Institute (WHRI) conference in Cannes, October 1998. Merck Research Laboratories also acknowledged this position in a published abstract; (Slegl *et al* 1999). In addition the literature on this subject acknowledged meloxicam as an NSAID with selectivity towards the COX-2 isoenzyme with

minimal effects on COX-1 activity. Boehringer Ingelheim thus alleged that the quoted findings of this small study in the booklet were not consistent with the overall scientific evidence on this subject.

Boehringer Ingelheim stated that its written dialogue with Merck Sharp & Dohme did little to alleviate its concerns regarding this issue but rather added weight to these concerns.

Merck Sharp & Dohme, in a letter to Boehringer Ingelheim, a copy of which was provided, pointed out that the supporting data on file for this assay was in the public domain and was in fact presented at the European League Against Rheumatism (EULAR) Congress held in Glasgow, June 1999, and published in the abstract booklet of this congress, as abstract 857 (Schwartz *et al*).

Abstract 857, co-authored by Merck Sharp & Dohme personnel and therefore obviously supported by the company, provided results for the percentage COX-1 inhibition by different NSAIDs in terms of the effects of the tested NSAIDs on TxB_2 (as presented in the graph in the Vioxx booklet). Urinary 11-dehydro TxB_2 results were also mentioned for meloxicam and diclofenac, but in terms of the magnitude of this effect, by either medicine, were not provided.

Boehringer Ingelheim stated that Merck Sharp & Dohme had referred to a recently published paper from the WHRI (Warner *et al* 1999) which contained the full results of the study mentioned in the WHRI Highlights booklet.

In the Warner paper, Merck Sharp & Dohme stated that the results for the WBA IC80 ratios supported its contention that meloxicam and diclofenac were similar in terms of their effects on COX-1 activity, where:

- IC_{80} ratios in the WBA assay for meloxicam = 0.27 and diclofenac = 0.32.
- Meloxicam and diclofenac were ranked 11th and 10th respectively in terms of inhibition of COX-2 relative to COX-1.

Merck Sharp & Dohme therefore concluded that both abstract 857, reporting results of the study (referred to in the Vioxx booklet as data on file), and the full results of the WHRI (Warner paper) supported the view of similarity between meloxicam and diclofenac in terms of their effects on COX inhibition.

Boehringer Ingelheim stated that both abstract 857 and the Warner paper, in its opinion, did not support the contention that meloxicam and diclofenac were similar in their effects on the COX-1 isoenzymes, for reasons presented below.

Abstract/Poster 857

Boehringer Ingelheim stated that Merck Sharp & Dohme had supplied supporting information in the form of a paper copy of the text for abstract 857.

This information was actually presented as a poster (poster 857) at the XIV EULAR Congress June 1999 and published in the abstract booklet of this conference the Annals of Rheumatic Diseases. Boehringer Ingelheim was aware that the content of the poster presented at EULAR differed significantly from that of the published abstract and provided a set of photographs of the poster from the EULAR Congress. Merck Sharp & Dohme had, at no point, made reference to the existence of this poster, nor of the significant differences between the poster and the abstract in terms of the information it contained. At no time had Merck Sharp & Dohme provided the full data of this study.

Boehringer Ingelheim stated that a comparison of the poster and the abstract showed there to be a number of important discrepancies in terms of report results. All information pertinent to platelet aggregation and bleeding time which were also investigated in this study and presented in the poster were omitted from the abstract. Arguably, these were more clinically relevant markers of COX-1 platelet activity than the degree of TxB_2 inhibition.

The abstract concluded rofecoxib was the 'only specific inhibitor of COX-2 without meaningful COX-1 inhibition'. Yet the poster, particularly Figure 5 (Platelet Aggregation), Table 2 (Bleeding Time) and the Summary of Results and Conclusions clearly showed that:

Meloxicam, like rofecoxib but unlike diclofenac, had effects comparable to placebo on platelet aggregation (hence indicating meloxicam and rofecoxib to have little effect on COX-1 activity, unlike diclofenac).

The bleeding time change from baseline was seen to change less with meloxicam than both doses of rofecoxib and diclofenac, suggesting, for this marker, meloxicam had a lesser effect on COX-1 activity than rofecoxib and diclofenac, although this difference was not statistically significant.

It would be reasonable to expect that if any parameter were to be chosen as a meaningful measure of COX-1 inhibition by an NSAID it would be the absence of a pathophysiological effect on platelet aggregation or an absence of prolongation of the bleeding time rather than a value of percentage inhibition of TxB_2 as detected in the serum or urine.

Thus, it would seem that Merck Sharp & Dohme had selectively identified this one assay. Even more concerning was that it had only presented those parts of the results that appeared to support its position. In doing so the totality of the data from this study was not given – a fact that it had failed to disclose, in the abstract or in written dialogue with Boehringer Ingelheim.

WHRI full results – Warner et al paper

The paper by Warner *et al* was based upon the work performed by the WHRI, one of the world's leading authorities in this area. However this paper did not support the contention that there was a high degree of similarity between meloxicam and diclofenac in terms of their effect on COX-1 nor similarities in their relative selectivity for COX-2 versus COX-1.

Merck Sharp & Dohme had failed to mention the main results, those of the William Harvey Modified Whole Blood Assay (WHMA) COX-1 assays for meloxicam and diclofenac. These results showed a clear difference between the two medicines:

IC_{50} ratios: meloxicam = 0.040, diclofenac = 0.3

IC_{80} ratios: meloxicam = 0.091, diclofenac = 0.23

Meloxicam and diclofenac were ranked 6th and 9th respectively in terms of inhibition of COX-2 relative to COX-1.

As the author explained in the Merck Sharp & Dohme sponsored 'Highlights' booklet, the human WBA, though having the advantage over other types of assay in that it took account of the plasma protein binding, had the disadvantage that the enzyme inhibitor was incubated with the COX-1 in platelets for a shorter time than with the COX-2 in monocytes. The WHMA overcame this by standardising the incubation time for both enzymes. Therefore the WHMA, a whole blood assay technique, was an improved version of the WBA method the results from which, given in the same paper, Warner *et al* (1999), were highlighted by Merck Sharp & Dohme in inter-company correspondence.

Additional results contained in Warner *et al* also showed the two NSAIDs, meloxicam and diclofenac, to differ in their effects on COX-1 activity. Thus: Figure 4 clearly showed a difference between the two NSAIDs in terms of the percentage inhibition of COX-1 when COX-2 (as determined by the WHMA) was inhibited by 80%. For meloxicam, approximately 30% COX-1 inhibition occurred when the COX-2 isoenzyme was inhibited by 80%, whilst with diclofenac under the same conditions of 80% COX-2 inhibition, approximately 70% COX-1 inhibition was seen. Figure 3 demonstrated a difference between the two NSAIDs in terms of their relative selectivity for COX-2 versus COX-1. Meloxicam was included in the group of NSAIDs between 5 to 50 fold COX-2 selective whilst diclofenac appeared in the <5 fold COX-2 selective group.

Conclusion

Merck Sharp & Dohme had stated to Boehringer Ingelheim that it believed that the COX-1/COX-2 assay data for Vioxx and meloxicam as presented on pages two and three of the booklet were a fair reflection of the results of Schwartz *et al*… and were consistent with the results presented in the WHRI paper.

After consideration of the complete results of the Warner paper, with knowledge of the full results of the Schwartz *et al* study as provided in poster 857 (but omitted in the abstract), and previous literature on the subject, it was clear that the COX inhibition section of the Vioxx booklet did not accurately reflect the data contained in the references quoted, nor was it consistent with an up-to-date evaluation of all the evidence on the topic of COX inhibition. Boehringer Ingelheim therefore alleged that this was a breach of Clause 7.2 of the Code.

RESPONSE

Merck Sharp & Dohme stated that its understanding was that the clauses of the Code dealing with comparative data envisaged a situation whereby the comparison was made between the respondent's promoted product and that of the complainant.

It would appear that Boehringer Ingelheim accepted that the claims made in relation to the relative inhibition of COX-2/COX-1 by Vioxx had been substantiated. Instead the company had focussed on the relative inhibition of COX-1 by meloxicam and diclofenac.

The way this piece would be used was to demonstrate that Vioxx, at the level of the human whole blood *ex vivo* assay, could already be differentiated from the competitor products that appeared in the graph presented in the promotional item. The relative ranking of the individual competitor products was not important as far as the promotion of Vioxx was concerned. It was a debate which would be superfluous to the promotion of Vioxx. Merck Sharp & Dohme was not saying that such an approach was licence to be misleading with regard to the relative ranking of competitor products, but it remained its contention that the natural interpretation of Clause 7 related to comparisons between the respondent's and the complainant's product.

Merck Sharp & Dohme stated that the graph represented data from Patrignani's human whole blood *ex vivo* assay to demonstrate the percentage inhibition of TxB_2 production, as a measure of COX-1 inhibition, for a selection of widely known NSAIDs. Merck Sharp & Dohme believed this whole blood *ex vivo* assay, after clinically relevant dosing, was the most physiological of the many assays currently available as it assessed activity of clinically relevant medicine and metabolite concentrations, in a physiological medium with locally derived substrate. For this reason, at the outset of the Vioxx clinical development programme, this particular assay was selected to assess COX-2/COX-1 inhibition.

The results from the study by Schwartz *et al* were presented at EULAR 1999 in the form of both a poster presentation and as abstract 857 contained within a journal supplement distributed at the meeting. The primary endpoint of the study was to determine the inhibition of TxB_2 production, as a measure of COX-1 inhibition, in a sample of blood taken from healthy volunteers on day 6, following 5 days of treatment with an NSAID. Secondary endpoints included inhibition of PGE2 production, as a measure of COX-2 inhibition, levels of excretion of urinary prostanoids, platelet aggregation and bleeding time. Boehringer Ingelheim alleged that not only did Merck Sharp & Dohme fail to provide the full data from this study, but that it had deliberately suppressed important data relating to platelet function which appeared in the poster presentation but not in abstract 857. This discrepancy in the data would appear to be one of Boehringer Ingelheim's major bones of contention. Merck Sharp & Dohme was therefore a little surprised that it did not explicitly raise this issue in its initial letter of complaint when it was clear that it was in possession of both the abstract data and photographs of the poster presentation. Had Merck Sharp & Dohme been asked specifically to provide the platelet function data, or indeed proffer an explanation as to why it had chosen not to present platelet data in the booklet, it would have provided the explanation that followed.

Platelet function, and the influence of Vioxx and NSAID comparators, notably meloxicam and

diclofenac, was evaluated by *ex vivo* stimulated platelet aggregation and *in vivo* bleeding times. The data from these evaluations were viewed in relation to the demonstrated fact that Vioxx and meloxicam, but not diclofenac, did not significantly affect platelet aggregation. Bleeding time relative to placebo was not influenced by any of the three medicines. This lack of obvious platelet aggregation by meloxicam was likely to be explained by a lack of a direct correlation between inhibition of platelet aggregation and platelet biosynthetic activity for TxB_2 generation during spontaneous coagulation. In addition the relatively high concentration of arachidonic acid used in the platelet aggregation assay might have influenced the ability to demonstrate subtle abnormalities in platelet function. Having highlighted the above qualifications required in order to interpret the platelet function results, it was important to view all the results that were obtained from the Schwartz study and not just the two points that were reported by Boehringer Ingelheim. The results were as follows:

1 Meloxicam, diclofenac, ibuprofen and naproxen all showed ≥ 50% inhibition for serum TxB_2; Vioxx demonstrated < 10%.

2 Vioxx did not significantly reduce urinary 11-dehydro TxB_2 relative to placebo. Meloxicam and diclofenac both significantly decreased urinary 11-dehyrdro TxB_2 excretion relative to placebo.

3 Platelet aggregation following Vioxx and meloxicam treatments was not significantly inhibited, while diclofenac, ibuprofen and naproxen significantly inhibited platelet aggregation.

4 Vioxx, meloxicam and diclofenac did not significantly affect bleeding time.

Merck Sharp & Dohme therefore proposed that when all of the above results were taken into consideration Vioxx could be clearly separated from the other NSAIDs and that any differences between meloxicam and diclofenac were not as clear cut as Boehringer Ingelheim suggested.

In addition, it would suggest that TxB_2 production as a measure of COX-1 activity, demonstrated using the *ex vivo* assay, was the most straightforward assay data to present to physicians to enable an understanding of the relative COX-2/COX-1 inhibition concept, which was undoubtedly a complex one. It therefore believed that the totality of the data supported the positioning of Vioxx and this was in line with the data presented in the graph. Furthermore, Merck Sharp & Dohme believed that the totality of the data demonstrated a high degree of similarity between meloxicam and diclofenac, consistent with the data presented in the booklet.

One further point was raised by Boehringer Ingelheim in relation to the data presented by Warner *et al.* The degree of COX-1 inhibition produced by the concentration of medicine required to inhibit COX-2 by 80% was the level suggested by Warner which represented the best comparison to the clinical situation in relation to therapeutic dosing. The results obtained ranked meloxicam and diclofenac as 6th and 9th when using the modified whole blood assay and 9th and 10th in the original whole blood assay. Neither of these results would appear to demonstrate a significant difference between treatments. However Merck Sharp & Dohme would suggest that the whole blood assays developed by Patrignani and used by Merck Sharp & Dohme in its clinical development programme for Vioxx represented one step closer to the clinical situation than that of Warner's modified whole blood assay. The rationale behind Patrignani's assay was that healthy volunteers were treated with an NSAID for 5 days before blood was drawn and assessed for the level of COX-1 inhibition. This therefore took account of all factors such as plasma protein binding and metabolite production that influenced what actually happened when the medicine was given to humans. The modified whole blood assay involved obtaining a blood sample from healthy volunteers without any recent prior exposure to an NSAID. NSAID test agent was then added to this blood sample followed by an assessment of COX-1 inhibition. Whilst the modified assay, developed by Warner and colleagues, took into account the different incubation periods used when assessing COX-1 versus COX-2 inhibition it believed that the results from the assay system by Patrignani, rather than this modified assay, most closely resembled the outcome of the clinical situation. It was therefore this system that was chosen to determine the effect of Vioxx on COX-1 and COX-2 and it was these results that were presented in the booklet. However, when all the results were compared across the board a clear trend could be identified which showed that Vioxx clearly exhibited different characteristics to those of other NSAIDs and that overall when the totality of the data was taken into account it was difficult to elucidate a clear distinction between diclofenac and meloxicam.

Finally, whilst Boehringer Ingelheim seemed to be accusing Merck Sharp & Dohme of 'cherry-picking' it seemed to be indulging in exactly the same practice in its selective citing of references to support its claim. This in itself did not represent the totality of the data between meloxicam and diclofenac and on closer inspection these references included studies in dogs, which it would suggest had only a rudimentary relevance to man, a reference that indicated meloxicam inhibited the production of TxB_2 by 66%, a value in line with the data presented in its graph and yet another reference stated that at concentrations producing more than 60% inhibition of PGE_2, meloxicam was found to be equipotent in the inhibition of COX-1 and COX-2. Furthermore, Brooks *et al* reported 'Thus depending on the assay, [meloxicam's] selectivity for COX-2 can vary 30 fold' versus the 10 fold variability suggested by Boehringer Ingelheim and Chan *et al* reported an index of relative COX-2 selectivity of rofecoxib > celecoxib > meloxicam ~/= diclofenac > indomethacin. It therefore suggested that the position of meloxicam on the selectivity ladder was not as clear cut as Boehringer Ingelheim would lead one to believe. But as far as Merck Sharp & Dohme was concerned, and in the context of how the above promotional piece would be used to promote Vioxx, it was irrelevant. However in the context of this specific complaint Merck Sharp & Dohme would assert that Boehringer Ingelheim was engaging in identical tactics to those that it had alleged it had used.

In summary, Merck Sharp & Dohme believed that it had been able to demonstrate that the data presented in the booklet was indeed a fair, balanced and accurate representation of the data not only for Vioxx but also for the relative positioning of meloxicam with diclofenac.

PANEL RULING

The Panel noted that pages two and three of the booklet compared the relative COX-1 and COX-2 inhibition of Vioxx, using the human whole blood *ex vivo* assay, with placebo and four competitor NSAIDs. The Panel did not accept Merck Sharp & Dohme's submission that the relative ranking of individual competitor products was not important as far as the promotion of Vioxx was concerned nor its contention that the natural interpretation of Clause 7 related to comparisons between the respondent's and the complainant's products. Clause 7 governed information, claims and comparisons regardless of whether such matters referred to the respondent company's product. Allegations concerning the relative ranking of meloxicam and diclofenac were thus within the ambit of Clause 7.

The Panel examined abstract 857 by Schwartz *et al* (1999) which assessed the inhibitory activity by rofecoxib on COX-2 versus COX-1 in comparison to meloxicam, diclofenac, ibuprofen and naproxen in 76 healthy female volunteers in a randomised partially blinded, placebo-controlled trial. COX-1 and COX-2 activity was measured using the whole blood *ex vivo* assay. The mean (time) weighted average COX-2 and COX-1 inhibition over eight hours for meloxicam was 77.5% and 53.3% and diclofenac 93.9% and 49.5%. The graphs on pages 2 and 3 of the booklet depicted these results although it was impossible to determine the precise figures from them. It was noted in the abstract that both diclofenac and meloxicam decreased urinary 11-dehydro TxB_2 whereas rofecoxib had no significant effect compared to placebo.

The Panel noted that the poster presentation provided more information about the study. Further details were provided about the assay method. It was stated that diclofenac, ibuprofen and naproxen were included for reference as NSAIDs that were well recognised dual COX-1/COX-2 inhibitors. Meloxicam was described as a cyclo-oxygenase inhibitor that had been claimed to possess some degree of selectivity for COX-2 versus COX-1.

The study authors concluded, *inter alia,* that neither platelet aggregation nor bleeding time were meaningfully altered by 12.5mg or 25mg rofecoxib or by meloxicam; whilst diclofenac was not associated with a detectable alteration in bleeding time it did inhibit platelet aggregation. Ibuprofen and naproxen substantially inhibited both measures of platelet function.

The Panel considered that differences between abstract, subsequent poster and final paper were not unusual and in this regard noted that the abstract featured only primary end point analyses whilst both primary and secondary analyses appeared in the poster. The Panel did not accept that a failure to include reference to secondary end points of bleeding time and platelet aggregation on pages 2 and 3 of the booklet in itself necessarily constituted a breach of the Code. The question to be decided was whether overall the data presented was fair, balanced and in accordance with Clause 7.2 of the Code.

The Panel considered that this was a complex area. Given that this was a developing area of science it was necessary to be cautious when making claims. There was some debate about how COX-1/COX-2 selectivity ought to be measured. It was noted that Brooks *et al* (1999) which had adopted the Patrignani assay methodology was a report of an international consensus meeting which sought to provide a definition of COX-2 specificity and to consider the clinical relevance of COX-2 specific agents. It was recommended, *inter alia*, that results from *in vitro* be used only as a guide to the relative *in vivo* selectivity of different NSAIDs studied in the same assay system. Reference was made to the variety and variability of in vitro COX isoforms. It was recommended that the 'Human whole blood assay' be used to determine COX specificity. The Panel noted that de Meijer *et al* (1999) stated that the bleeding time test was inherently variable and was not very sensitive for inhibition of COX-1.

The Panel noted that Warner *et al* (1999) assessed the selectivity for COX-1 and COX-2 of newer and classical NSAIDs, including diclofenac and meloxicam, using the human whole blood assay and a modified human whole blood assay. Meloxicam and diclofenac were ranked 9th and 10th using the whole blood assay and 6th and 9th using the modified whole blood assay.

Brooks *et al* (1999) stated, *inter alia,* that in the MELISSA trial (n=10,000) meloxicam and diclofenac demonstrated similar efficacy. When discussing the variability of *in vitro* assay systems for determining COX-2 specificity, Brooks *et al* noted that depending on the assay system used meloxicam's selectivity for COX-2 could vary 30 fold. Chan *et al* (1999) stated that in the human whole blood assay selectivity ratios for the inhibition of COX-2 produced an index of rofecoxib > celecoxib > meloxicam ~/= diclofenac > indomethacin.

The Panel considered that the purpose of the pages at issue was to present the data on the selectivity of Vioxx compared to other NSAIDs based on the results of Schwartz *et al*. A clear statement about the assay method used appeared in a highlighted box. The Panel considered that the relative positioning of meloxicam and diclofenac fairly reflected the finding of Schwartz *et al*. The Panel noted that some studies had indicated differences between meloxicam and diclofenac. Such differences varied depending on the assay method etc. The Panel considered that on balance the data presented was not inconsistent with the overall scientific evidence.

The Panel did not accept that the graphs were misleading as alleged and ruled no breach of Clause 7.2 of the Code.

Complaint received **23 December 1999**

Case completed **30 March 2000**

CASE AUTH/967/1/00

PRIMARY CARE GROUP PRESCRIBING SUPPORT PHARMACIST v SCHWARZ PHARMA

Promotion of Tylex

A prescribing support pharmacist to a primary care group complained about an item promoting Tylex (paracetamol 500mg and codeine phosphate 30mg) issued by Schwarz Pharma.

The item referred to the cost of the branded combination and the cost of its generic components prescribed separately. One page gave the prescribing cost to the NHS including dispensing fees, container allowance and ingredient cost per 100 tablets or capsules. The cost for Tylex was given as £9.24 and the cost of paracetamol and codeine prescribed separately was £10.52. The item claimed that Tylex was 12% lower in cost than the component medicines.

The complainant alleged that the item was misleading and not wholly accurate. While it was cheaper to prescribe Tylex than the separate components, the complainant did not believe that pharmacist fees should be included as it made no difference to overall NHS costs whether it was ordered as a compound or separately. It would make a difference to an individual pharmacist who would receive one or two fees but the total amount of money paid to the nation's pharmacists to dispense the nation's prescriptions, called the global sum, was fixed.

Tylex was not 12% cheaper to the NHS than the component medicines, the actual figure according to the complainant was 6%.

The Panel noted that the ingredient cost of Tylex was £8.21 and the generic versions of the component medicines cost £8.46. The Panel noted that the global sum was fixed each year. Any surplus was shared out amongst pharmacists and any shortfall was clawed back from pharmacists. The dispensing of the component medicines might be a contributing factor to any increase in global sum but this would not be known until the next year's global sum had been fixed. In the Panel's view it was too simplistic to include the dispensing fees in the calculation to support the claim that Tylex cost 12% less than the individually prescribed components. The effect of the dispensing fee and the container allowance was more complicated than the impression given. The Panel ruled that the item was misleading.

A prescribing support pharmacist to a primary care group complained about a promotional item for Tylex (paracetamol 500mg and codeine phosphate 30mg) issued by Schwarz Pharma Limited. The item had been used as an insert in Pulse, 17 December 1999, mailed to target pharmaceutical advisers, primary care group prescribing leads and clinical governance leads. It had also been used by representatives in detailing general practitioners. The cover of the four page A4 item stated 'This branded combination analgesic more expensive than its generic components prescribed separately?' with 'Poppycock!' beneath it. On page 3 the total prescribing cost to the NHS, including dispensing fees, container allowances and ingredient cost per 100 tablets or capsules, was given in a table as £9.24 for Tylex and a total of £10.52 for paracetamol and codeine prescribed separately. The claim 'Tylex Capsules: now 12% lower in cost than equivalent, individually prescribed generic paracetamol and generic codeine tablets' appeared immediately above the table.

Text above the table stated 'Moreover, unlike Tylex Capsules, individually prescribed paracetamol tablets and codeine tablets attract two pharmacist dispensing fees and two container allowances. The savings to the NHS of prescribing and dispensing Tylex Capsules is therefore greater than General Practitioners might first imagine'.

COMPLAINT

The complainant alleged that the item was misleading and not wholly accurate. Whilst it was true that it was currently cheaper to prescribe Tylex Capsules than ordering the components separately, the complainant did not believe that pharmaceutical companies should involve pharmacist fees in their advertising. This was because it actually made no difference to overall NHS costs whether any compound preparation was ordered as such, or as its separate components. Yes, it made a difference to the pharmacist who actually dispensed the prescription (whether they would receive one or two professional fees) but the total amount of money paid to the nation's pharmacists in professional fees to dispense the nation's prescriptions was fixed. It was called the global sum. If fewer prescriptions were dispensed than anticipated, any surplus was actually shared out among pharmacists. If more items were dispensed than anticipated, there was a 'clawback', and each prescription was paid for at a slightly lower rate. The Pharmaceutical Services Negotiating Committee, (PSNC) should be able to confirm this. There were therefore no savings (to overall NHS costs) to be made by prescribing single ingredients, or multi-ingredient preparations.

Thus, the claim 'The savings to the NHS of prescribing and dispensing Tylex Capsules is greater than General Practitioners might at first imagine' was not strictly true, and the table presented was misleading. Tylex was not 12% cheaper to the NHS than equivalent individually priced ingredients; the actual figure was nearer 6%.

The complainant stated that Schwarz should withdraw the advertisement or at least not be permitted to involve dispensing pharmacists' fees in its calculations.

RESPONSE

Schwarz stated that the PSNC had provided the following information:

- The global sum was the total amount of money paid by the Department of Health (DoH) each year for the nation's pharmacists to cover professional fees, including the dispensing fee and container allowance, during that year. The amount each year was fixed.

- The amount provided by the DoH in the form of the global sum depended on negotiations between the PSNC and the DoH, but the Secretary of State for Health had the final decision on the amount provided, so he might not accept recommendations from the PSNC.

- The Secretary of State for Health considered the following information provided by the PSNC when setting the global sum:

– number of pharmacists in the country;

– inflation rates;

– volume of dispensing fees, including the container allowance, and

– dispensing fees claimed over the previous year,

as well as certain other factors.

It was true that if the volume of dispensing fees claimed from the global sum increased during the year the dispensing fees had to fall to accommodate this as the global sum was fixed.

However, an increased volume of dispensing fees over the preceding year influenced the global sum set for the next year. Therefore the cost to the NHS could increase. Multiple ingredient prescriptions versus single prescriptions for combination products would result in higher volume of dispensing fee claims during the year.

Each prescription attracted a dispensing fee of 97.5p and 5.6p container allowance (November 1999 Drug Tarriff). The cost and the number of fees received by the pharmacist dispensing paracetamol 500mg and codeine 30mg tablets were therefore twice that of dispensing Tylex.

This influenced the global sum set for the following year and hence the cost to the DoH and the NHS.

General practitioners were being advised to prescribed Tylex components separately. This would have a marked effect on the volume and value of dispensing fees claimed by pharmacists and subsequently result in an increase in the global sum which came from NHS funds.

Schwarz Pharma considered that the claim 'Tylex Capsules: now 12% lower in cost than equivalent, individually prescribed generic paracetamol tablets and generic codeine tablets' was therefore a true reflection of the cost difference and not misleading or inaccurate.

PANEL RULING

The Panel noted that the difference between the cost per 100 of Tylex Capsules and its component medicines had been highlighted in the first section of the table. The ingredient cost was £8.21 for Tylex Capsules and £8.46 (£0.60 + £7.86) for paracetamol 500mg plus codeine 30mg. It was therefore cheaper to use Tylex Capsules than generic versions of the component medicines.

The Panel noted all the comments made about the global sum. The position was complicated. As the Panel understood it, the amount paid to pharmacists for dispensing prescriptions was fixed each year. This figure might change each year depending on circumstances. It appeared to the Panel that although individual pharmacists might benefit from dispensing the component medicines as two dispensing fees would be claimed, this would not effect NHS spending as a whole as the global sum was fixed each year. The dispensing of the component medicines might be a contributing factor to any increase in the global sum but this would not be known until the next year's global sum had been fixed. The Panel noted that, according to The Pharmaceutical Journal, 14 August 1999, in 1998/99 there had been an underpayment which had been distributed to contractors as a lump sum.

In the Panel's view, it was too simplistic to include the dispensing fees in the calculations to support the claim that Tylex Capsules now cost 12% lower than individually prescribed generic paracetamol and generic codeine. The effect of the dispensing fee and container allowance on NHS costs was more complicated than the impression given.

The Panel considered that the item was misleading as alleged and a breach of Clause 7.2 of the Code was ruled.

Complaint received **4 January 2000**

Case completed **10 February 2000**

CASES AUTH/969/1/00 & AUTH/973/2/00

HOSPITAL CONSULTANT v CENTOCOR and SCHERING-PLOUGH

Report on Remicade

A hospital consultant complained about a report which detailed various aspects of Remicade (infliximab) in Crohn's disease which had been presented at a European conference. The report had been sent by a medical education agency purporting to be an independent professional news service. The document allegedly summarised a debate entitled 'Is anti-TNF-α antibody the magic bullet for Crohn's disease?' of which Remicade was the subject but presented a gross misrepresentation of what had taken place. It was not mentioned that anyone spoke against the motion or that the audience overwhelmingly voted against the motion. The report contained no details of how to contact the agency nor was it stated that the agency was acting on behalf of Centocor. The complainant stated that he had never seen such a blatant misrepresentation of the truth on behalf of a pharmaceutical company.

Centocor BV was the licence holder for Remicade in the UK but the product was distributed by Schering-Plough. Centocor had had nothing to do with the report and the Director decided that it had no *prima facie* case to answer.

The Panel noted that Schering-Plough had engaged the agency to prepare and distribute a report on those treatment areas of interest to the company which were discussed or presented at the conference. Despite the contractual arrangements between the parties which stated that the agency was responsible for the balance and accuracy of the report and would retain editorial control, Schering-Plough had influenced the content of the report and so was responsible for its compliance with the Code. If this were not so then companies could pay third parties to write and distribute reports which they as companies could not and so avoid the restrictions of the Code.

The report only presented favourable data on Remicade. In the Panel's view the report was promotion for Remicade and had to meet the requirements of the Code. The Panel considered that the report did not provide a fair, accurate or balanced account of the debate at issue. The report did not contain prescribing information. Breaches of the Code were ruled.

The Panel considered that the report gave the impression that it was an independent publication, an impression strengthened by use of the agency logo and the statement that the agency was an independent, professional news service. There was no reference to either Schering-Plough or Centocor. In the Panel's view the report was disguised promotion for Remicade which failed to declare company sponsorship. Breaches of the Code were ruled. Overall the Panel considered that high standards had not been maintained and a breach of the Code was ruled in that regard.

A hospital consultant submitted a complaint about a report concerning the United European Gastroenterology Week, Italy, November 13-18 1999, distributed by a medical education agency.

The report was headed 'Anti-TNF-α to cure Crohn's disease.' The introductory paragraph stated that Remicade (infliximab) had been chosen as the subject for the 'magic bullet debate' and that this gave a strong indication that Remicade would be an important therapy in the next millennium. Remicade was an anti-TNF agent and the debate was entitled 'Is anti-TNF-α antibody the magic bullet for Crohn's disease?' A short synopsis of the debate was given and then the report detailed 'Selected clinical posters on anti-TNF Remicade therapy', 'Remicade and closing fistulae,' 'Clinical data in paediatric Crohn's disease' and the 'Long-term safety of Remicade.' All of the data presented on Remicade was favourable.

Centocor BV was the licence holder for Remicade in the UK but it had an agreement with Schering-Plough for the distribution of the product in Europe. Schering-Plough stated that it was responsible in collaboration with Centocor for the production and distribution of promotional material and other associated activities. The matter was initially taken up with Centocor (Case AUTH/969/1/00) whereupon the Director decided that there was no *prima facie* case for the company to answer under the Code as Centocor had had nothing to do with the report. The matter was subsequently taken up with Schering-Plough Ltd.

COMPLAINT

The complainant stated that the report was sent to him by a medical education agency purporting to be an independent professional news service. The document allegedly summarised a debate on anti-TNF antibody. The complainant stated that he had been present at the debate and the report was a gross misrepresentation of what had taken place. For example it was not mentioned that a doctor spoke against the motion and that a vote taken of the audience was overwhelmingly also against the motion. There was no address or contact number for the medical education agency on the report, nor did it state whether it was acting on behalf of Centocor which manufactured Remicade, but this was undoubtedly the case. The complainant stated that he was moved to write because he had never in his career seen such a blatant misrepresentation of the truth on behalf of a pharmaceutical company.

RESPONSE

Schering-Plough stated that it had been in discussion with Centocor and noted the response provided by Centocor to the Authority. Schering-Plough confirmed that it had provided an educational grant to the agency which published the report for the

purpose of covering treatment areas of interest to Schering-Plough discussed or presented at the meeting. The grant was not for the purpose of promoting Remicade or any product in particular, nor was it intended that any publication arising would provide a promotional vehicle for Remicade.

The agency was an independent company that prepared reports, in the form of medical education updates, covering current medical data and opinion, as presented at medical meetings. These reports were intended to be objective, balanced and scientifically rigorous. As an independent news service, the agency retained editorial and distribution control over its publications and was solely responsible for the content of the report, for assuring objectivity and balance. This was defined in the conditions of the blanket agreement, a copy of which was provided, which covered activities of this type and which ceded all editorial rights to the agency.

Schering-Plough did not direct or influence the content of the report, nor did it have the right to do so. Indeed, the agreement specifically stated that the sponsor, Schering-Plough '…agrees not to engage in scripting, selecting points for emphasis, or engaging in any activities designed to influence the content of the Report.' The agency agreed that it would '…take steps to insure that data will be objectively selected and presented'. And that 'Favourable and unfavourable information shall be fairly represented'. Schering-Plough had relied on the agency to present such a report on the debate in question.

The conference was a scientific meeting covering a broad range of subjects with particular attention paid to the clinical problems related to digestive disease. The debate in question,'Is anti-TNF-a antibody the magic bullet for Crohn's disease?', was chaired by an American professor and two debators, both doctors, spoke for and against the motion respectively. Schering-Plough understood that much of the argument against centred on the appropriateness of the term 'magic bullet' rather than the specific scientific merits of the treatment of Crohn's disease with anti-TNF-α. The speaker for the motion mainly discussed the science of the therapy. The speaker against the motion focussed on what any medicine needed to accomplish to be considered a 'magic bullet'. He described requirements that would need to be satisfied, such that no medicine – including penicillin – could be considered likely to fulfil the criteria and therefore qualify for the 'magic bullet' status.

It would seem that the reporter detailed by the agency to cover this symposium reported on the various presentations of scientific information regarding anti-TNF-α of which the debate was only one aspect. His discussion of the debate focused on the more specific aspects of the science of infliximab, omitting reference to the discussions relating to 'magic bullet' status.

Schering-Plough stated that it had discussed this matter directly with the agency and it confirmed that the report was reviewed through its normal procedures before distribution to physicians. The agency maintained that the report was accurate with respect to reporting of the scientific details; It accepted, however, that inclusion of reference to the debate required coverage of the dissenting side of the debate for a well-balanced report.

Schering-Plough had taken steps to ensure that future activities of this type were more strictly controlled, whilst not restricting the freedom of organisations like the agency in question to exercise editorial independence in communication of information to members of the medical profession.

PANEL RULING

The Panel noted that the report had been prepared and distributed by an agency. A pro forma agreement between the agency and a sponsor had been provided which stated that 'Both parties agree that the report is for scientific and educational purposes and not for the purpose of promoting any particular product'. The agency would ensure that 'data will be objectively selected and presented. Favourable and unfavourable information shall be fairly presented – both for any sponsor marketed product or any competitor product covered in the presentations reported on, in a balanced and meaningful fashion.' The agreement further stated that the agency was solely responsible for the content of the report and the sponsor agreed, *inter alia*, not to engage in any activity designed to influence the content of the report. It was further stated that 'The [financial] support [of the sponsor] shall be clearly acknowledged on the report'.

Clause 9.9 required material relating to medicines to so declare if it had been sponsored by a pharmaceutical company and this applied even if the material was non-promotional. The content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose. Even if neither of these applied, the company would be liable if it had been able to influence the content of the material. It was possible for a company to sponsor material which mentioned its own products and not be liable under the Code for its content, but only if the material was non-promotional in nature and it had been a strictly arm's length arrangement with no input by the company and no use by the company of the material for promotional purposes.

The Panel noted that Schering-Plough had paid the agency, a commercial organisation, to prepare and distribute a report on those treatment areas of interest to the company which were discussed or presented at the meeting. The Panel noted Schering-Plough's submission that it had no editorial control. The Panel noted that despite the contractual arrangements between the agency and Schering-Plough, Schering-Plough was responsible for compliance with the Code. If this were not so then it would be possible for companies to pay independent third parties to write and distribute reports which they, as companies, could not write and so avoid the restrictions of the Code.

The intended audience was not clear. The report had been mailed to physicians, such as the complainant who had attended the conference. The Panel noted that Centocor stated that the report was mailed to an audience of physicians selected by the agency.

The Panel noted that the report referred to the debate 'Is anti-TNF-α antibody the magic bullet for Crohn's disease?' but only reported what had been said in favour of the motion. The report only presented favourable clinical data on Schering-Plough's product, Remicade. Unfavourable data and other products were not mentioned. The Panel noted the complainant's submission that a vote taken of the audience was overwhelmingly against the motion. The report referred to the product as having impressive effectiveness, a spectacular healing response and appearing to be effective and safe in children. In the Panel's view the report was promotion for Remicade and had to meet the requirements of the Code. The Panel considered that the report did not provide a fair, accurate or balanced account of the debate at issue and a breach of Clause 7.2 was ruled. The report failed to contain prescribing information as required by Clause 4.1 of the Code. A breach of that clause was also ruled.

The Panel considered that the report gave the impression that it was an independent publication. This impression was strengthened by the agency logo which appeared on the front page in the top right hand corner and a footnote to each page which stated, *inter alia*, that the agency was 'an independent, professional news service that reports on worldwide current medical meetings.' There was no reference to either Schering-Plough or Centocor. In the Panel's view the report was disguised promotion for Remicade. A breach of Clause 10.1 was ruled.

The Panel noted that the supplementary information to Clause 10.1 referred to the need for companies to declare sponsorship on company sponsored material as required by Clause 9.9 of the Code. No such declaration appeared on the report. A breach of Clause 9.9 was ruled.

Overall the Panel considered that high standards had not been maintained and a breach of Clause 9.1 was ruled.

Complaint received **13 January 2000**

Case completed **23 March 2000**

CASE AUTH/974/2/00

GENERAL PRACTITIONER v GALDERMA

Differin and Eryacne 'Dear Doctor' letter

A general practitioner complained that a 'Dear Doctor' letter sent by Galderma promoting Differin and Eryacne was in breach of the Code. The non-proprietary name for Differin was given on the front of the letter whereas the non-proprietary name for Eryacne was not.

Galderma apologised for the error. The Panel ruled a breach of the Code as the non-proprietary name for Eryacne had not been given immediately adjacent to the most prominent display of the brand name as required by the Code.

A general practitioner complained about a 'Dear Doctor' letter sent by Galderma (UK) Limited. The letter was headed 'The Differin approach' with a sub-heading of 'Develop your Differin approach with Eryacne'. The Differin logo with the non-proprietary name, adapalene, and the strapline 'A baseline therapy for acne', appeared in the bottom right-hand corner of the letter. The prescribing information for both products appeared on the reverse of the letter.

COMPLAINT

The complainant stated that the letter appeared to be promoting two products: Differin was identified by both its approved and trade name, however Eryacne Gel was only identified by its trade name. The name Eryacne Gel appeared seven times in the letter, so the complainant concluded that the purpose of the letter was to promote both Differin and Eryacne.

Since there was no mention of the approved name on the front of the letter, the complainant suspected that Galderma was in breach of the Code.

RESPONSE

Galderma stated that it was strongly committed to upholding the highest standards in relation to its advertising of prescription only medicines and endeavoured to ensure that all promotional material was produced in accordance with the provisions of the Code. It was with much regret therefore, that the company accepted that the mailing concerned was in breach of Clause 4.2 of the Code; this was a simple error, which unfortunately went unnoticed at all stages of the copy approval process.

The company did not consider that there was any breach of Clause 4.1 of the Code. Prescribing information, clearly showing the approved names for both products, was printed on the reverse and the location of this was clearly indicated at the foot of the front page of the letter. The company stated that this was not an attempt to mislead, or in any other way, misrepresent its products.

Galderma stated that the mailing had not been repeated and was not being used in any other format by its marketing department or field sales force; the company gave an assurance that no further breaches of the Code would result from this simple error. Galderma stated that it had taken the opportunity to stress to all members of the promotional material

generation and approval process within the company, the importance of double-checking all copy prior to its despatch from the company.

PANEL RULING

The Panel noted that the 'Dear Doctor' letter contained several references to Eryacne Gel but that the only reference to erythromycin, the non-proprietary name, was in the prescribing information printed on the back of the letter. The Panel noted that Clause 4.2 of the Code listed the component parts of the prescribing information and, in addition, stated that the non-proprietary name or a list of active ingredients must appear immediately adjacent to the most prominent display of the brand name in not less than 10 point bold or in a type size which occupied a total area no less than that taken by the brand name. Clause 4.1 of the Code stated that the information listed in Clause 4.2 must be provided. Failure to do so would therefore be a breach of this clause and not of Clause 4.2. The failure to include the non-proprietary name immediately adjacent to the most prominent display of the brand name, which in the Panel's view was the sub-heading of the letter, meant that Galderma had not complied with Clause 4.1 and a breach of that clause was ruled.

Complaint received **4 February 2000**

Case completed **13 March 2000**

CASE AUTH/975/2/00

SMITHKLINE BEECHAM v BAYER

Ciproxin cost comparison

SmithKline Beecham complained about a cost comparison in a Ciproxin detail aid issued by Bayer. The cost comparison related to the treatment of respiratory tract infections (RTIs) in general practice and listed the costs of available patient packs of Ciproxin (ciprofloxacin) and co-amoxiclav (SmithKline Beecham's product Augmentin). The cost of 5 days' treatment with Ciproxin was compared with that of 7 days' treatment with co-amoxiclav. It was alleged that this was unfair as co-amoxiclav was usually given for 5 days in RTIs.

In the Panel's view the cost comparison would be taken to represent the cost of treating a patient with an RTI. Readers would assume that the only treatment courses which should be prescribed were those consistent with the patient packs listed and so treatment with co-amoxiclav was likely to always be more expensive than with Ciproxin. The summary of product characteristics (SPC) for Augmentin stated that the duration of therapy should be appropriate and should not exceed 14 days without review. The only patient packs listed in the cost comparison for co-amoxiclav were those for 7 day courses. Co-amoxiclav was, however, available in bulk packs so that doctors could be flexible in the quantity they prescribed. Market data showed that five day courses were used.

The Panel considered that the cost comparison failed to adequately reflect the information in the Augmentin SPC regarding duration of treatment. By omitting the cost of a five day course the data did not reflect current usage of co-amoxiclav. The Panel considered that the cost comparison was misleading and a breach of the Code was ruled.

SmithKline Beecham Pharmaceuticals complained about a page in a Ciproxin (ciprofloxacin) detail aid (ref 9CIPR135) issued by Bayer plc Pharmaceutical Division. The page was headed 'How does the cost of Ciproxin compare' and featured a table entitled 'Cost per patient pack'. Costs were given for Ciproxin (250mg x 10; 250mg x 20; 500mg x 10; 500mg x 20; 750mg x 10), co-amoxiclav (375mg x 21; 625mg x 21; 1g x 14) and clarithromycin (250mg x 14; 500mg XL x 7; 500mg XL x 14; 500mg x 14). The cost of the smallest patient pack of Ciproxin (£7.50) was less than the smallest patient pack of co-amoxiclav (£9.79). A footnote beneath the table read 'For the treatment of RTIs [respiratory tract infections] in General Practice'.

SmithKline Beecham marketed Augmentin (co-amoxiclav).

COMPLAINT

SmithKline Beecham noted that pack sizes indicated in the cost comparison table compared 5 days' treatment with Ciproxin and 7 days' treatment with co-amoxiclav with an indication that these were the doses for the treatment of respiratory tract infection in general practice. SmithKline Beecham considered that this was an unfair comparison, in breach of Clause 7.2 as Bayer was not comparing like with like. The usual dose of co-amoxiclav in this indication was 3 times daily for 5 days and these prices should have been quoted for this comparison not vs 7 days.

RESPONSE

Bayer stated that it considered that the comparison was fair and compared like with like. The table was clearly headed 'Cost per patient pack'. It compared the costs of all the available patient packs of Ciproxin, co-amoxiclav and clarithromycin.

The first patient pack size stated for each product was the smallest and least expensive available on the market. Subsequent columns of data detailed all other available patient packs.

Bayer considered that by adopting this depiction it had fairly represented the range of potential prescribing

costs incurred in the use of these products. This was similar to the approach commonly adopted in MIMS and would be familiar to most potential prescribers.

Bayer accepted that the exact cost of any given therapy was a function not entirely of the cost per patient pack but also of the dosage and duration of treatment specified. In the field of antimicrobial prescribing there existed considerable variation with regard to recommended licensed dosages and course length, dependent upon indication. For example in respiratory tract infections Ciproxin might be prescribed 100-750mg twice daily for 5-10 days, co-amoxiclav 375mg three times daily for up to 14 days or in severe infections, 625mg three times daily or 1g twice daily. Clarithromycin had an equally broad dosing regime. The clinical judgement of the physician would be the ultimate determinant of the dosage and duration prescribed and thus the total cost of therapy.

Bayer stated that its representatives were instructed to ask the prescribers which dose of Ciproxin and its comparators they commonly used. The representative was then able to use the table to help the GP identify the comparative cost of his choices with respect to the available pack sizes and strengths. Bayer considered that this was a clear and fair way to represent cost in a complicated area.

With regard to what constituted the 'usual' dose of co-amoxiclav in respiratory infections, Bayer stated that its data source (DIN-link) suggested that there existed a wide variation in the dose and duration of therapy written by GPs and that these might sometimes differ from those recommended by the summary of product characteristics (SPC).

Bayer stated that the most commonly written prescription for 375mg co-amoxiclav it could identify in respiratory tract infections (upper and lower) was 21 tablets, accounting for some 60% of these prescriptions in 1999. Where those prescriptions were written by brand then this proportion was even higher. It seemed eminently appropriate then that the smallest patient pack available of co-amoxiclav, produced by SmithKline Beecham, was 375mg x 21 tablets.

Bayer stated that it was unsure upon what basis SmithKline Beecham concluded that the usual dose of co-amoxiclav in this indication was 3 times daily for 5 days. Bayer considered that only 30% of prescriptions were 375mg x 15 tablets (DIN-link MAT December 1999). However, if in the future SmithKline Beecham was to produce a patient pack to support this prescription size then Bayer would of course include it in its information.

Bayer stated that its aim had been to fairly reflect, within the representative discussion, the prescriber's individual variations by relating all cost discussions back to the common reference of the available patient packs. The table did not attempt to relate individual comparative dosages of products rather the company had sort to portray the full range available.

To this end, Bayer submitted that the item in question was not in breach of Clause 7.2. The table was clearly headed 'Cost per patient pack' and represented an unambiguous and fair comparison of the range of such costs as they might be incurred by potential prescribers.

PANEL RULING

The Panel noted that the cost of the smallest patient pack of co-amoxiclav was more than the cost of the smallest patient pack shown for Ciproxin. Similarly the next two sizes of patient packs for co-amoxiclav were more expensive than the next two sizes of patient packs for Ciproxin respectively. A footnote to the cost comparison table stated 'For the treatment of RTIs in General Practice'. A claim beneath the table stated 'Use of Ciproxin could lead to potential cost savings.' In the Panel's view the table would be taken to represent the cost of actually treating a patient with a respiratory tract infection. Readers would assume that the only treatment courses which should be prescribed were those consistent with the patient packs listed, and so treatment with co-amoxiclav was likely to always be more expensive than with Ciproxin.

The Panel referred to the SPCs published in the ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1999-2000. The Augmentin (co-amoxiclav) SPC stated that for the treatment of infection in adults and children over 12 years, the usual dose of the product was 375mg three times a day which could be increased to 625mg three times a day in severe infections. It was stated that the duration of therapy should be appropriate to the indication and should not exceed 14 days without review. (For dental infections the duration of therapy was given as 5 days).

The SPC for Ciproxin, supplied by Bayer, stated that in adults the dose range for the treatment of respiratory tract infections was 250-750mg twice daily depending on severity. The usual treatment period was 5-10 days.

The Panel noted that the cost comparison chart listed patient packs for Ciproxin consistent with 5 or 10 day courses of treatment. The only packs listed for co-amoxiclav were those consistent with 7 day courses of treatment. The Panel noted, however, that co-amoxiclav 375mg was available in packs of 100 tablets and so doctors were not restricted to only prescribing patient packs; they could be flexible in the quantity they prescribed. The Panel noted that when prescriptions were written for co-amoxiclav in respiratory tract infections, 60% were for 325mg x 21 tablets ie 7 days' supply and equivalent to the smallest patient pack. 30% of prescriptions, however, were for 325mg x 15 ie 5 days' supply which would be taken from a pack of 100; the cost of this prescription would be £7.08 and therefore less expensive than a five day course of Ciproxin 250mg twice daily (£7.50).

The Panel considered that the cost comparison table failed to adequately reflect the information in the Augmentin SPC regarding the duration of treatment. By omitting the cost of a five day course the cost comparison also did not reflect current usage of co-amoxiclav. The Panel considered that the cost comparison was misleading. A breach of Clause 7.2 was ruled.

Complaint received **7 February 2000**

Case completed **21 March 2000**

CASE AUTH/976/2/00

NOVO NORDISK v SOLVAY

Femoston-conti journal advertisement

Novo Nordisk complained about a Femoston-conti (estradiol and dydrogesterone) journal advertisement issued by Solvay. The advertisement stated that 'With new Femoston-conti you can be reassured that: the cardiovascular benefits of oestradiol will be maintained' and 'dydrogesterone is the only oral progestogen which does not negate the positive effect of oestrogen on HDL-cholesterol'.

Novo Nordisk alleged that the advertisement promoted the cardiovascular benefits and this was an unauthorized indication. The advertisement was also alleged to be misleading as it was thought that less than 50% of the possible effect of hormone replacement therapy (HRT) in reducing the risk of cardiovascular disease was through changes in lipid and lipoprotein metabolism and no mention was made of the role of triglycerides.

The Panel noted that Femoston-conti was a low dose HRT licensed for relief of menopausal symptoms and for prophylaxis of post-menopausal osteoporosis in women at risk of developing fractures. There was no mention of cardiovascular effects in the indications. The Panel considered that the layout and content of the advertisement was such that the cardiovascular outlook appeared to be an indication and the reason for prescribing and not a consequence of treatment. The Panel ruled that the advertisement promoted an unlicensed indication in breach of the Code. The advertisement was too positive with regard to the cardiovascular benefits given that the summary of product characteristics (SPC) referred only to the beneficial effects of oestrogen on lipids and lipoproteins and that the consequential impact of such effects on cardiovascular risk factors was not stated. A breach of the Code was ruled.

Novo Nordisk Pharmaceuticals Ltd complained about an advertisement (ref SOL 76/12/99B) for Femoston-conti (estradiol and dydrogesterone) issued by Solvay Healthcare Limited. The advertisement appeared in Pulse 15 January. It was headed 'When she chooses freedom from periods … how does your choice affect her cardiovascular outlook?' The advertisement then stated 'With new Femoston-conti you can be reassured that: the cardiovascular benefits of oestradiol will be maintained' and 'dydrogesterone is the only oral progestogen which does not negate the positive effect of oestrogen on HDL-cholesterol'. This was followed by the brand name in large letters and the claim 'Low dose HRT for the post-menopausal woman'.

COMPLAINT

Novo Nordisk stated that the effects of hormone replacement therapy (HRT) on the cardiovascular system had been the subject of research and discussion for several years. However, a consensus had not yet appeared and HRT was not approved for prevention or for treatment of cardiovascular disease. The effects and possible benefits of HRT on the cardiovascular system should be categorised under 'Emerging clinical or scientific opinion' as mentioned in supplementary information to Clause 7.2.

The advertisement stated that 'The cardiovascular benefits of oestradiol will be maintained'. This implied that Femoston-conti had cardiovascular benefits, and taking the advertisement as a whole most of the text was concerned with cardiovascular effects.

Whilst Novo Nordisk believed it was legitimate to provide information on emerging clinical or scientific opinion in a balanced way, this advertisement went beyond this and actively promoted cardiovascular benefits. It was thus promoting an unauthorized indication in breach of Clause 3.2 of the Code.

In addition, the statements in the advertisement were unbalanced and misleading in that current opinion concerning the relative importance of the various risk factors for cardiovascular disease was not mentioned. Thus, whilst the advertisement described the effect of Femoston-conti on certain lipid levels, it was now thought that less than 50% of the possible effect of HRT in reducing the risk of cardiovascular disease was through changes in lipid and lipoprotein metabolism. Furthermore, no mention was made of changes in other lipids such as triglycerides, which were considered to be an independent risk factor, and were known to be altered by HRT. The advertisement was therefore alleged to be in breach of Clause 7.2 of the Code.

RESPONSE

Solvay stated that it had experienced considerable difficulty in understanding the exact nature of Novo Nordisk's concerns, particularly in view of the fact that the beneficial effects of HRT on cardiovascular disease risk factors were highlighted in Novo Nordisk's own promotional material. The problem was compounded by the conflicting opinions expressed in the letter of complaint regarding the current state of knowledge on the effects of HRT on the cardiovascular system. These varied from 'a consensus has not yet appeared' to 'it is now thought that less than 50% of the possible effect of HRT in reducing the risk of cardiovascular disease was through changes in lipid and lipoprotein metabolism'.

None of these points, however, seemed to have a direct bearing on the advertisement which legitimately provided information on the pharmacodynamic features of Femoston-conti. The message being conveyed was that the progestogen, dydrogesterone, had no influence on the beneficial effects of oestrogen. Furthermore, the statements were entirely consistent with the summary of product characteristics (SPC) which stated that 'The beneficial effects of 17ß-estradiol on bone, lipoprotein, glucose and insulin metabolism are maintained in the

presence of dydrogesterone' and were supported by a wealth of data.

Solvay stated that adverse changes in lipoprotein, glucose and insulin metabolism were seen following the menopause and might affect a woman's cardiovascular outlook. For example, low levels of high density lipoprotein (HDL)-cholesterol, the 'good' cholesterol, were the best predictor of coronary heart disease risk in women. Oestrogen used alone prevented or reversed some of these adverse changes. The addition of the progestogen, dydrogesterone, did not influence these oestrogenic effects. In particular, dydrogesterone did not reverse the favourable oestrogen-induced increase in HDL-cholesterol.

In view of the continuing confusion regarding the role of HRT in preventing or treating cardiovascular disease (as illustrated in the complainant's letter), Solvay had been extremely careful in the advertisement to avoid any suggestion that the product could or should be used for these indications. The licensed indications were clearly stated on the advertisement. The pharmacodynamic properties of the medicine were listed as referenced bullet points and were clearly points of information and not indications for use. Solvay did not accept that the advertisement was in breach of Clause 3.2 of the Code.

Solvay also did not accept that the statements in the advertisement were in any way unbalanced or misleading. The statements were completely accurate and unambiguous. The complaint's implied criticism that Solvay presented unbalanced information by highlighting the effects of oestrogen on HDL-cholesterol rather than on triglycerides, was unfounded. As discussed above, the current consensus was that HDL-cholesterol was the best predictor of coronary heart disease (CHD) risk in women. Each 1% increase in HDL-cholesterol levels reduced CHD risk by approximately 3%. It had been suggested that up to half of the apparent cardiovascular benefit observed in oestrogen-treated women might be mediated by the higher HDL-cholesterol levels.

In contrast, there was no consensus on the significance of the elevation in triglyceride levels seen with oestrogen alone (and with oestrogen in combination with dydrogesterone). The rise in triglyceride levels appeared to be due to increased production rather than to the decreased elimination seen in association with familial hypertriglyceridaemia and the changes might, in fact, not be atherogenic. Bush *et al*, for example, showed that oestrogen treatment in women with high levels of cholesterol and triglycerides was associated with a reduction in mortality, despite causing a further elevation in serum levels of triglycerides.

Since the possible impact of oestrogen-induced rise in triglyceride levels on CHD risk in the post-menopausal woman had not been ascertained, it would be completely inappropriate to take a position on the role of triglycerides as risk factors in advertising material. Solvay therefore did not accept that the advertisement breached Clause 7.2 of the Code.

PANEL RULING

The Panel noted that Femoston-conti was low dose HRT for women with a uterus who were more than 12 months post-menopausal. The product was licensed for relief of menopausal symptoms and for prophylaxis of post-menopausal osteoporosis in women at risk of developing fractures. There was no mention of cardiovascular effects in the indications. Section 5.1 of the SPC stated that the oral administration of oestrogens had a beneficial effect on the metabolism of lipids and lipoprotein. The SPC also stated that the beneficial effects of 17ß-estradiol on bone, lipoprotein, glucose and insulin metabolism were maintained in the presence of dydrogesterone

The Panel noted that the advertisement discussed the cardiovascular outlook of women; the description of the product as 'Low dose HRT for the post-menopausal woman' appeared as a strapline at the bottom of the advertisement. The actual indications for the product ie relief of menopausal symptoms or the prophylaxis of post-menopausal osteoporosis, only appeared in the prescribing information.

The Panel considered that the emphasis on the cardiovascular outlook had not been placed in context. The layout and content was such that the cardiovascular outlook appeared to be an indication and the reason for prescribing Femoston-conti and not a consequence of treatment with the product for the licensed indications.

On balance the Panel considered that the advertisement promoted an unlicensed indication and a breach of Clause 3.2 of the Code was ruled.

With regard to the alleged breach of Clause 7.2 of the Code the Panel noted that it was now thought that about 50% of the cardiovascular benefit associated with HRT was mediated through changes in lipid and lipoprotein metabolism. The position with regard to triglycerides was less certain. The Panel noted that the Femoston-conti SPC referred to the beneficial effects of oestrogen on lipids and lipoproteins; the consequential impact of such effects on cardiovascular risk factors was not stated. Given the statements in the SPC the Panel considered that the advertisement was too positive with regard to the cardiovascular benefits of Femoston-conti; readers would assume that the product had a significant positive clinical effect. The Panel considered that in this respect the advertisement was misleading and ruled a breach of Clause 7.2 of the Code.

Complaint received **8 February 2000**

Case completed **30 March 2000**

GENERAL PRACTITIONER v SCHERING HEALTH CARE

Femodene e-MIMS advertisement

A general practitioner complained about an advertisement for Femodene issued by Schering Health Care. The advertisement had appeared in e-MIMS and showed the top half of a young woman whose bust was wrapped in a packet of Femodene. The complainant stated that he would not want to call up the image if he was discussing contraception with a patient; he found it offensive and he was sure most doctors would too.

The Panel noted that the young woman wore a wide bandeau which bore the image of a foil pack of Femodene; no more was revealed than her shoulders and three or four inches of bare midriff. The banner advertisement continuously scanned down the picture, dividing it into three parts; the Panel was concerned that the final part rested, albeit briefly, on the image of the young woman's bust. The Panel accepted that the complainant had found the advertisement offensive but did not consider that that would be the general reaction. There was an element of sexual imagery but the Panel considered that on balance the advertisement was not unacceptable in this regard. No breach of the Code was ruled.

A general practitioner complained about an advertisement for Femodene (ethinyloestradiol and gestodene) issued by Schering Health Care Limited and placed on the February 2000 CD ROM of e-MIMS.

COMPLAINT

The complainant alleged that the advertisement contravened Clause 9.1 of the Code, quoting the supplementary information to that clause which referred to types, styles and methods of promotion which were unacceptable for medicines as including:

- the display of naked or partially naked people for the purpose of attracting attention to the material or the use of sexual imagery for that purpose
- 'teaser' advertising whereby promotional material is intended to 'tease' the recipient by eliciting an interest in something which will be following….

The complainant stated that the advertisement was accessed by clicking start, disease, contraception and combined oral contraceptives and the advertisement appeared in a window in the top right hand corner of the screen. It showed the top half of an attractive woman in her late teens or early twenties whose bust was wrapped in a packet of Femodene. Since the window was wider than it was long the young lady's face appeared first. The window then panned down over her body and stopped at the waist. Clicking on the advertisement gave a view of the whole top half of the woman's body.

The complainant would not want to call the image up onto his screen if he was discussing contraception with a patient – particularly a modern politically correct woman or a member of a religious or ethnic minority; he found it offensive and he was sure most doctors would as well.

RESPONSE

Schering Health Care stated that the complainant contended, in particular, that the material infringed the Code on the basis of two examples given in the supplementary information, ie the use of naked or semi-naked people for the purpose of attracting attention to the material, and the inappropriateness of so-called 'teaser' advertising.

As far as the latter was concerned, Schering Health Care believed that the complainant had misinterpreted the meaning of 'teaser' in the context of the Code. 'Teaser' advertising was used to elicit interest in something, for example, a product, details of which would follow only at a later date, and did not initially provide information about the product. The complainant might, in fact, consider that the word 'teaser' implied some sexual connotation, but Schering Health Care did not believe that this was so. The e-MIMS advertisement contained all of the information about Femodene required by the Code even if it did not show it immediately, which was analogous to many other promotional items, such as leavepieces, which might not carry the name of the product on the front cover.

The main basis of the complaint was, Schering Health Care believed, the supplementary information prohibition on the display of naked (which was clearly irrelevant in this case) or semi-naked people for the purpose of attracting attention to the material or the use of sexual imagery for that purpose. There were a number of elements to be considered:

Was the model semi-naked or not? The use of the expression 'semi-naked' was, to a certain extent, a value judgement. The model in the advertisement was wearing a bandeau, which was a current fashion worn extensively by young women (Femodene's target users) in public places all over the country. While it did not cover the upper body fully, Schering Health Care disputed that the model could be described as 'semi-naked'.

Was this sexual imagery? It followed from what was said above that Schering Health Care also disputed that any sexual imagery had been used. The advertisement portrayed a young woman wearing contemporary fashion. If it was accepted that this was 'sexual imagery', it was difficult to conceive of a situation in which Schering Health Care, as manufacturers of oral contraceptives, could produce material in which normal users of its products could be shown.

Was the purpose of the semi-naked display to attract attention to the material? As stated above, Schering Health Care did not consider that the model was semi-naked, but it recognised that that was, to a certain extent, a value judgement. Therefore, even assuming that the model could be described as 'semi-

naked', Schering Health Care disputed that the purpose of that portrayal was for the purpose of attracting attention to the material. The messages that this material was intended to convey were as follows:

(i) the use of the foil displayed the Schering calendar pack, which Schering Health Care considered to be a very useful aid to compliance;

(ii) the display of the calendar pack was done in a way that demonstrated the 'close fit' to the woman's needs, ie the suitability of the product (hence the 'suits her' strap-line); and

(iii) the use of the imagery conveyed a modern, up-to-the-minute feel for the product (as mentioned above, bandeaux were currently very popular) which encouraged confidence in the brand as moving with the times.

Complaints based on Clause 9 of the Code were often very difficult to assess, but if the Panel were to consider whether the advertisement was likely to cause offence to a significant number of readers Schering Health Care would contend that it did not do so. The reason for this contention was that the material had been used in one form or another since April 1999 and this was the first complaint that had been received. The complainant claimed to be offended, and attempted also to attribute similar offence to unspecified 'politically correct women or a member of a religious or ethnic minority'. Schering Health Care did not believe that this attribution of offence by the complainant was justified and the Panel should consider the complaint only on the basis that this one GP was offended.

PANEL RULING

The Panel noted that 'the display of naked or partially naked people for the purpose of attracting attention to the material or the use of sexual imagery for that purpose' was a method of promotion proscribed by the supplementary information to Clause 9.1 of the Code. The Panel noted that the banner advertisement was divided into three parts. The first part was a photograph of the woman's face and the statement 'suits', followed by 'her' a few seconds later. The second part was of the shoulders and upper chest including the upper part of the bandeau. The third part, at which the banner came to a brief halt before starting again, showed the lower part of the bandeau and a small section of bare midriff and the statement 'Right from the start Femodene'. The banner continuously scanned down the image of the young woman. The whole advertisement which was accessed by clicking on the banner showed the whole image of the woman (from her head to her waist) wearing a bandeau which bore the image of the foil pack of Femodene. The bandeau was a wide one and the illustration revealed no more than the shoulders and three or four inches of bare midriff. The Panel did not consider that this amounted to the model being shown as either naked or partially naked.

The reference to 'teaser' advertising by the complainant was considered by the Panel to be misplaced as this related to an advertisement which referred to something which would follow at a later date without providing any actual information about it. This was not the position here.

The Panel was concerned that the final part of the banner came to rest albeit briefly on the image of the woman's bust wrapped in the Femodene bandeau.

The Panel accepted that the complainant had found the advertisement offensive but did not consider that that would be the general reaction. There was an element of sexual imagery but the Panel considered that on balance the advertisement was not unacceptable in this regard in view of the purpose of the product and the age and gender of those who might use it. No breach of the Code was ruled.

Complaint received **16 February 2000**

Case completed **23 March 2000**

CODE OF PRACTICE REVIEW – MAY 2000

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

895/7/99	**Pfizer v Schwarz Pharma**	**Sponsored publication – ED Matters**	**Breach Clause 2 Six breaches Clause 7.2 Two breaches Clause 7.3 Breaches Clauses 7.7 and 7.10 Three breaches Clause 8.1 Publicly reprimanded by ABPI Board**	**No appeal Reported to ABPI Board**	**Page 3**
902/7/99	Trustees of the National Asthma & Respiratory Training Centre v Boehringer Ingelheim	Sponsorship of the Respiratory Education Resource Centres	No breach	Appeals by complainant and respondent	Page 9
914/8/99	**Monmouth v Merck Sharp & Dohme**	**Promotion of Vioxx**	**Two breaches Clause 7.2**	**Appeal by complainant**	**Page 21**
919/8/99	**Schering Health Care v Guerbet**	**Xenetix letter**	**Breaches Clauses 4.1, 9.4 and 15.2**	**Appeal by complainant**	**Page 30**
927/9/99	**Pharmaceutical Adviser v AstraZeneca**	**Educational meeting**	**Breaches Clauses 7.2, 8.1 and 10.1**	**Appeals by complainant and respondent**	**Page 34**
936/9/99	**General Practitioner v Roche Consumer Health**	**Rennie Duo 'Dear Doctor' letter**	**Breach Clause 7.2**	**Appeal by complainant**	**Page 44**
938/10/99	**The National Pharmaceutical Association v Trinity**	**Sales methods**	**Breach Clause 8.2**	**Appeal by respondent**	**Page 46**
947/10/99	**Director v Bristol-Myers Squibb**	**Presentation at a meeting**	**Breach Clause 7.2**	**Appeal by respondent**	**Page 49**
955/11/99	General Practitioner v Merck Sharp & Dhome	Cancelled meeting	No breach	No appeal	Page 54
956/11/99	**Lilly v Janssen-Cilag**	**Promotion of Risperdal**	**Breach Clause 7.2**	**No appeal**	**Page 56**
958/11/99	**Allergan v Pharmacia & Upjohn**	**Xalatan leavepiece**	**Two breaches Clause 7.2**	**No appeal**	**Page 60**
959/11/99	**Director v Guerbet**	**After sales service**	**Breach Clause 18.1**	**No appeal**	**Page 62**
960/12/99	**Director v Pierre Fabre**	**Promotion of Navelbine**	**Breach Clause 3.2**	**No appeal**	**Page 64**
961/12/99	**Pharmaceutical Adviser v AstraZeneca**	**Sponsorship of evidence based workshop**	**Breach Clause 9.9**	**No appeal**	**Page 67**
963/12/99	**University Clinical Reader v Reckitt & Colman**	**Buccastem mailing**	**Breach Clause 7.2**	**No appeal**	**Page 68**
964/12/99	**AstraZeneca v Wyeth**	**Promotion of Zoton and failure to comply with undertaking**	**Two breaches Clause 7.2 Breach Clause 21**	**No appeal**	**Page 69**
965/12/99	Boehringer Ingelheim v Merck Sharp & Dohme	Promotion of Vioxx	No breach	No appeal	Page 73

967/1/00	**Primary Care Group Prescribing Support Pharmacist v Schwarz Pharma**	**Promotion of Tylex**	**Breach Clause 7.2**	**No appeal**	**Page 78**
969/1/00 & 973/2/00	**Hospital Consultant v Centocor and Schering-Plough**	**Report on Remicade**	**Centocor: no *prima facie* breach Schering-Plough: Breaches Clauses 4.1, 7.2, 9.1, 9.9 and 10.1**	**No appeal**	**Page 80**
974/2/00	**General Practitioner v Galderma**	**Differin and Eryacne 'Dear Doctor' letter**	**Breach Clause 4.1**	**No appeal**	**Page 82**
975/2/00	**SmithKline Beecham v Bayer**	**Ciproxin cost comparison**	**Breach Clause 7.2**	**No appeal**	**Page 83**
976/2/00	**Novo Nordisk v Solvay**	**Femoston-conti journal advertisement**	**Breaches Clauses 3.2 and 7.2**	**No appeal**	**Page 85**
978/2/00	General Practitioner v Schering Health Care	Femodene e-MIMS advertisement	No breach	No appeal	Page 87

PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

The Prescription Medicines Code of Practice Authority was established by The Association of the British Pharmaceutical Industry (ABPI) in 1993 to operate the Code of Practice for the Pharmaceutical Industry at arm's length from the ABPI itself.

Compliance with the Code is obligatory for ABPI member companies and, in addition, about seventy non member companies have voluntarily agreed to comply with the Code and to accept the jurisdiction of the Authority.

The Code covers the advertising of medicines to health professionals and administrative staff and also covers information about such medicines made available to the general public.

It covers:

- journal and direct mail advertising
- the activities of representatives including detail aids and other printed material used by representatives
- the supply of samples
- the provision of inducements to prescribe, supply or buy medicines by the gift, offer or promise of any benefit or bonus, whether in money or in kind
- the provision of hospitality
- the organisation of promotional meetings
- the sponsorship of scientific and other meetings including payment of travelling and accommodation expenses in connection therewith
- the provision of information to the general public either directly or indirectly
- all other sales promotion in whatever form, such as participation in exhibitions, the use of audio-cassettes, films, records, tapes, video recordings, electronic media, interactive data systems, the Internet and the like.

Complaints submitted under the Code are considered by the Code of Practice Panel which consists of the three members of the Code of Practice Authority acting with the assistance of independent expert advisers where appropriate. Both complainants and respondents may appeal to the Code of Practice Appeal Board against rulings made by the Panel. The Code of Practice Appeal Board is chaired by an independent legally qualified Chairman, Mr James Hunt QC, and includes independent members from outside the industry.

In each case where a breach of the Code is ruled, the company concerned must give an undertaking that the practice in question has ceased forthwith and that all possible steps have been taken to avoid a similar breach in the future. An undertaking must be accompanied by details of the action taken to implement the ruling. Additional sanctions are imposed in serious cases.

Complaints about the promotion of medicines should be sent to the Director of the Prescription Medicines Code of Practice Authority, 12 Whitehall, London SW1A 2DY (telephone 020 7930 9677 facsimile 020 7930 4554).