PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

NUMBER 19 FEBRUARY 1998

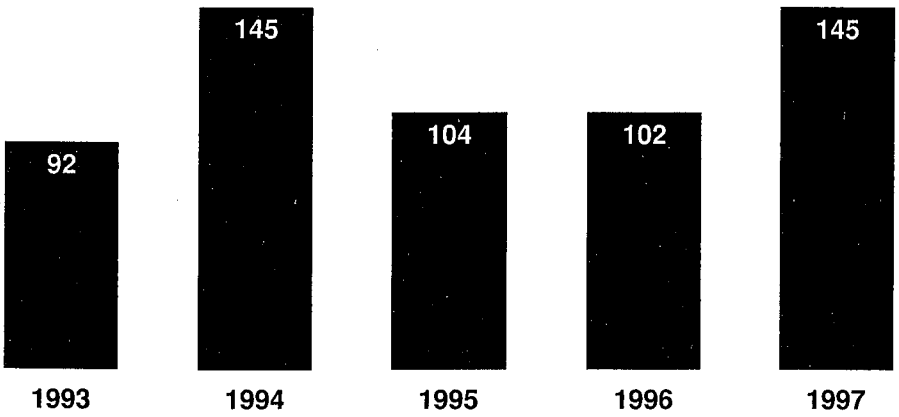
The Prescription Medicines Code of Practice Authority was established by The Association of the British Pharmaceutical Industry (ABPI) in 1993 to operate the ABPI Code of Practice for the Pharmaceutical Industry independently of the Association itself.

Complaints up in 1997

1997 saw an increase in the number of complaints made under the Code of Practice as compared with 1996. There were 145 complaints in 1997 and 102 in 1996. Some complaints give rise to more than one case as allegations are made against more than one company. At 166, the number of cases dealt with in 1997 exceeded that in any previous year.

In 1996 for the first time the number of inter-company complaints exceeded the number received from health professionals, 46% coming from companies and 40% from health professionals. In 1997 there was a return to the usual pattern with 52% of complaints coming from health professionals and 33% from companies.

The five years since the Authority was established at the begining of 1993 have shown wide and unexplained swings in the number of complaints received each year, ranging from 92 in 1993 to 145 in 1994 and 1997.



1998 Edition of the Code now out and about

Companies are reminded that the 1998 edition of the Code of Practice for the Pharmaceutical Industry came into operation on 1 January and should now be in use by all those concerned with promotion. Bulk orders for copies have been met and anyone requiring further copies should contact Vicki Meyrick at the Authority.

New syllabus for representative examinations

The syllabus for the ABPI representative examinations is currently under review and the ABPI anticipates that a new edition will be published this summer.

The examinations to be held on 11 May and 2 November this year will be based on the current syllabus. The May 1999 examinations will be based on the forthcoming new edition.

All pharmaceutical companies are reminded that representatives must pass either the Generic Sales Representatives Examination or the Medical Representatives Examination, as appropriate, before completing more than two years as a representative, whether with one company or with more than one and whether as continuous service or not. Full details of the requirements are given in Clause 16 of the Code.

Meetings and hospitality - Clause 19

Companies are reminded that they must have procedures in place to ensure that all meetings which are planned comply in all respects with the Code, in particular with Clause 19. These procedures should cover a company's own meetings, those which it sponsors and the sponsorship of attendance at meetings.

Representatives should be provided with written instructions on the application of the Code to their work even if they are also provided with an actual copy of it. The instructions should cover the company's policies on meetings and hospitality. Attention is drawn to the Guidelines on company procedures relating to the Code of Practice (page 37 of the Code of Practice booklet). Those Guidelines state that a system should be in place for an audit on a systematic or random basis which will check the nature of representatives' expenditure and assess whether that expenditure was in accordance with the requirements of the Code.

Clear complaints make for clear rulings

It is sometimes the case that inter-company complaints are difficult to disentangle because the letter of complaint refers to previous correspondence between the parties. This can occasionally lead to a failure to take all of the allegations into proper account.

A letter of complaint should set out clearly and in full all of the allegations which the company concerned is making.

Correspondence which is provided can be referred to but should not be a substitute for a detailed letter of complaint.

It is in the interests of the complainant, the respondent and the Authority for all the issues to be dealt with to be set out clearly and completely in the first instance.

Companies are reminded that complaints should be signed by the chief executive.

Comparative advertising

After years of discussion about comparative advertising in the EU, "Directive 97/55/EC of the European Parliament and of the Council of 6 October 1997 amending Directive 84/450/EEC concerning misleading advertising so as to include comparative advertising" has been adopted and must be implemented by member states by April 2000 at the latest.

Comparative advertising is already permitted in the United Kingdom and is covered by the Code of Practice but some member states do not allow it or circumscribe it so as to make it impractical.

Implementation of the Directive in the UK will be kept under review and adjustments may be needed in due course to the requirements of the Code of Practice.

Visitor from South Africa

Kerry Ganter, Head of Professional & Educational Affairs of the Pharmaceutical Manufacturers Association of South Africa, spent two weeks with the Authority in January studying the Code of Practice and its operation. The South African pharmaceutical industry in currently in the process of implementing a new code.

During her stay, Kerry visited Astra Pharmaceuticals Ltd and Glaxo Wellcome UK Limited to see how companies operate so as to ensure their compliance with the Code. Kerry also attended an in-house seminar on the Code of Practice run by the Authority for a pharmaceutical company and one of the Authority's regular seminars at the Royal Society of Medicine.

CODE OF PRACTICE TRAINING

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

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

Forthcoming Code of Practice seminar dates are:

Wednesday, 29 April 1998
Wednesday, 13 May 1998
Thursday, 25 June 1998

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

For further information regarding any of the above, please contact Vicki Meyrick for details (0171-930 9677 extn 1443).

How to contact the Authority

Our address is:

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

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

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

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

Heather Simmonds: 0171-747 1438
Etta Logan: 0171-747 1405
Jane Landles: 0171-747 1415

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

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

ASTHMA NURSE AND GENERAL PRACTITIONER v ASTRA

Sponsored meeting on asthma

An asthma nurse and a general practitioner complained separately about an educational meeting sponsored by Astra. The audience consisted of general practitioners and asthma nurses and the meeting was entitled "Inhaled steroids to grow up with". The speaker was a consultant chest physician. The asthma nurse alleged that the talk was not well balanced. It emphasised side-effects with fluticasone at high doses. The general practitioner considered that to be alarmist about the side-effects of a product when it was being used at 10 times its recommended dose was unfair to the product which might have an important role in improving the management of asthma.

The Panel noted that according to the information before it, the presentation centred around the speaker's research regarding the use of high dose fluticasone in children and the observed growth retardation in these patients. The Panel considered that the meeting was unbalanced and disparaged fluticasone. Too much was being made of available data. Breaches of the Code were ruled.

On appeal by Astra, the Appeal Board noted that no judgement was being made in relation to the speaker's professional integrity. The question to be answered was whether or not it was appropriate for Astra to have sponsored the meeting. The Appeal Board noted that the growth retardation in children on high doses of inhaled steroids was one part of a four part presentation. High dose inhaled steroids were referred to in the BTS guidelines for the treatment of asthma and prescription data showed that the use of high dose inhaled steroids was not uncommon in children. The Appeal Board considered that the talk was not unbalanced and nor did it disparage fluticasone. No breach of the Code was ruled.

Two health professionals complained separately about an educational meeting sponsored by Astra Pharmaceuticals Ltd. The audience consisted of GPs and asthma nurses. The meeting was PGEA approved and entitled "Inhaled steroids to grow up with". The speaker was a consultant chest physician.

COMPLAINT

Case AUTH/551/5/97

An asthma nurse said that she was concerned that this was a very biased talk singling out a Glaxo Wellcome product, fluticasone, stating that it was the most unsafe inhaled steroid with serious side-effects.

One of the examples given by the speaker was a young boy on high doses of fluticasone (1000mcg daily). This dose was well above the maximum paediatric dose according to the product licence. The boy subsequently had an adrenal crisis. The audience was misled into thinking that this was not unusual with fluticasone, by stating that there had been two other episodes of adrenal crisis reported. To the complainant's knowledge these two other cases were both in patients being treated with budesonide. Although the speaker was aware of this he seemed reluctant to divulge this to the audience.

The complainant said that it was known that high doses of inhaled steroids might have side-effects, but this was a class effect. The message from the speaker was that this only occurred with fluticasone and that Glaxo Wellcome was misleading people with its advertising of this drug.

In the complainant's view the talk was not well balanced. The complainant considered that the emphasis of the talk was to frighten general practitioners and practice nurses into not using fluticasone. The complainant was concerned that a pharmaceutical company was allowed to do this about another company's product.

Case AUTH/552/5/97

A general practitioner said that the speaker spoke well and with conviction but gave the impression that he considered that fluticasone was a potentially dangerous drug and that Glaxo Wellcome was withholding information about its safety profile. The complainant pointed out that the audience was a group of GPs and asthma nurses who were familiar with the product in recommended doses of 100 or 200mcg daily in children. At this dose growth suppression had not been seen. In children with severe asthma it was sometimes necessary to prescribe higher doses of fluticasone but in these circumstances the children should be attending a hospital asthma clinic and being monitored by a paediatrician who would be weighing the risks and benefits of using the medication outside recommended doses.

The British National Formulary made it quite clear that the upper limit of dose in children was 200mcg a day.

The complainant considered that to be alarmist about the side effects of a product when it was being used at 10 times the recommended dose was unfair to the product which might have an important role in improving the management of asthma.

RESPONSE

Astra submitted that it had had no input to, or editorial control over, the content of the presentation which was centred around the speaker's published research. A copy of a published paper was provided and an abstract together with copies of his slides.

Astra said that on speaking to the speaker after the receipt of these two complaints he had commented that at the beginning of his presentation he had made it clear that his research concerned the use of inhaled steroids in the minority of children who required high doses. Where these doses were outside the licensed range he had emphasised the upper dose limit of the product concerned. He was very surprised that any member of the audience could have misunderstood this.

Case AUTH/551/5/97

Astra addressed three specific points as follows:

1 ".....a biased talk, singling out a Glaxo Wellcome product, fluticasone, stating that it (fluticasone) was the most unsafe inhaled steroid with serious side effects."

Astra said that according to the speaker these were neither his words nor his views.

2 Misled the audience into believing that adrenal crisis was not unusual with fluticasone propionate

Astra said that according to the speaker, this was not at all what he said. One of his patients experienced an adrenal crisis on fluticasone propionate. The speaker made the observation that there were only two previously reported cases which had been associated with inhaled steroids in the literature. In doing so he was making the point that this type of event was extremely rare, given the extensive use of inhaled steroids over more than 25 years. There was no suggestion that these cases were all associated with the use of fluticasone propionate.

3 Implied that side effects at high doses were not class effects but occurred only with fluticasone propionate

It was extremely unlikely that any GP or practice nurse would be unaware that growth inhibition was a class effect of high dose inhaled corticosteroids, indeed this was a very common concern of patients. In the speaker's study, growth suppression was more pronounced with fluticasone propionate than with budesonide. Data from other published studies was shown which clearly illustrated that effects on hypothalmic-pituitary-adrenal (HPA) function were a class effect.

Case AUTH/552/5/97

Astra considered that the points raised here had been covered above. In his presentation the speaker was absolutely explicit that his case reports described the minority of children attending hospital clinics who required high doses of inhaled steroid to control their asthma. According to the speaker, he ensured that he gave a balanced view of his research.

Astra drew attention to the fact that in a previous case (Case AUTH/270/2/95) the Panel had ruled that a clinician was entitled to hold his own opinions and to express them. The views expressed by the speaker were his own and were fully supported by published literature including his own research. In response to a request for further information Astra confirmed that it had paid a honoraria fee for speaking. Astra strongly denied that any breach of the Code had occurred as a result of this meeting.

PANEL RULING

The Panel noted its ruling in a previous case (Case AUTH/270/2/95) as referred to by Astra. In that case the Panel had accepted that a speaker at a meeting was, as with any clinician, entitled to hold his own views and express them. The Panel had considered that 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 educational meetings. It was not possible, however, 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. It would be expected that a company in approaching a speaker to make a presentation at a sponsored meeting would be aware of the general views and opinions of the speaker and the likelihood that those views would be expressed in their presentation at the meeting. Otherwise it was unlikely that the speaker would be so invited. The case had gone to appeal. The Appeal Board had agreed with the Panel's views and had noted that the question was not whether it was appropriate for the speaker to have made the presentations but whether or not it was appropriate for the company to have sponsored them.

With regard to the case now before it, the Panel noted that the speaker had written to the Authority about his talk. The speaker acknowledged that the talk was controversial in that part of it challenged the claim that fluticasone was safer than the other inhaled steroids. The speaker was confident that his talk was neither misleading nor factually inaccurate.

The Panel examined the slides. There was of course no way of knowing what had been said at the meeting. One of the slides gave data regarding drug safety discontinuations in the UK, USA and Spain between 1947 and 1993 and stated that 29 drugs had been discontinued, 27 due to adverse reactions and 2 due to studies.

The Panel noted that the presentation centred around the speaker's research regarding the use of high dose fluticasone ($\geq$ 1000mcg/day) in children and the observed growth retardation in these patients. The published paper gave details about six children with growth retardation noted after treatment with high dose fluticasone propionate who were found to have adrenal suppression. The paper stated that "when high doses (substantially exceeding data sheet recommendations of 200mcg/day) of fluticasone were given as a dry powder, systemic levels may be sufficient to cause growth retardation and adrenal insufficiency". An abstract presented to the American Thoracic Society in May 1997 gave details about five severely asthmatic children with severe adrenal suppression and stated that ".... in severely asthmatic children it is confirmed that FP [fluticasone propionate] may cause serious adrenal suppression". The Panel noted that the doses of fluticasone used had exceeded the maximum licensed dose of the medicine in children (200mcg/day, ref ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1996-97).

The Panel noted that the meeting had been sponsored by Astra and that the company had invited and paid for the speaker. The views of the speaker would have been well known to Astra. The Panel considered that if the content of the presentation was unacceptable in terms of the Code then Astra was responsible. In this regard, the Panel noted that the Code covered information about medicines and the sponsorship of scientific meetings which would include meetings such as in this case.

The Panel noted that the presentation for Astra detailed growth problems in children following the use of high, unlicensed, doses of a competitor product. The Panel considered that in this respect the content of the meeting was unbalanced and ruled a breach of Clause 7.2 of the Code. Too much was being made of the available data. In addition the Panel considered that the critical references made to fluticasone were not fair as the doses used had been above those licensed for use in children. The Panel considered that the content of the meeting had disparaged fluticasone and ruled a breach of Clause 8.1 of the Code. The rulings applied to both cases.

APPEAL BY ASTRA

Astra said that the presentation described growth problems in children following the use of high, unlicensed, doses of fluticasone in children. The Panel had considered that in this respect the content of the meeting was unbalanced.

Astra asked the speaker to talk about asthma in general at a sponsored meeting arranged by a local representative. It was aware of his opinions and interests in growth retardation with inhaled steroids. However, the reason the speaker was invited was because of his knowledge of inhaled steroids and their use in asthma. The company had not briefed the speaker and nor had it seen copies of the slides. The objectives of the meeting were to communicate the benefits of inhaled steroids, discuss how to assess/compare different inhaled steroids, stimulate clinical/scientific debate and to support the use of budesonide. There was only one speaker at the meeting.

The talk did not centre around children being given large doses of fluticasone. The presentation was divided into four parts. The first part of the presentation dealt with one year benefits of all inhaled steroids. The third part discussed pharmacokinetics of all steroids and the fourth part comparative studies of all steroids. Only in one quarter of the presentation did the speaker discuss his published paper, and even so in that quarter the cases described had received unlicensed doses of both budesonide and fluticasone. The speaker prefaced this part of his talk by asking the delegates whether they knew what the licensed doses of budesonide, fluticasone and beclomethasone were, to clarify this point. He then went on to tell them that he would talk about unlicensed doses.

Astra disagreed that "too much was being made of available data". This part of the data only comprised a quarter of the talk, and was published in The Lancet, the world's premier journal. There were no other published studies of the effects of fluticasone on growth at comparable doses to those used by the speaker, and so this was the balance of evidence.

With regard to the Panel's view that the critical references made to fluticasone were not fair as the doses used had been above those licensed for use in children, Astra pointed out that the maximum licensed dose for children aged 4-15 years was 200mcg/day. Many prescriptions in this age group were for higher unlicensed doses and Astra provided information as to the number of such prescriptions and the proportion of the total that they represented. Astra believed that the speaker had highlighted a potentially significant area of concern and did not accept that his references to the effects of out of licence doses of fluticasone were unfair or disparaging.

Astra stated that the speaker was very concerned about the implications of this case for the independence of medical speakers at company sponsored meetings. He had also been contacted directly by Glaxo Wellcome regarding his involvement with Astra sponsored meetings. Astra shared his concern about the case as it held many meetings with invited medical speakers who did not necessarily represent Astra's views.

At the appeal, Astra provided information as to the proportions of prescriptions for patients 4-9 years old and for patients 10-15 years old which were for a daily dose of fluticasone of above 200mcg. Use of high dose inhaled steroids in children was established clinical practice. The British Guidelines on Asthma Management (1997) (known as the BTS Guidelines) included doses of inhaled steroids in excess of licensed recommendations both in children under 5 years of age and in adults and school children.

The speaker said that he had given the same talk on approximately 25-30 different occasions to over 1,000 doctors, including hospital specialists, paediatricians, authors of BTS guidelines and opinion leaders in the USA. The views on high dose inhaled steroids comprised one part of a four part talk. The speaker said that following his presentation some members of the audience had specifically and persistently questioned him about high dose inhaled steroids and growth retardation in children, a topic which had not formed a major part of his talk.

APPEAL BOARD RULING

The Appeal Board noted that no judgement was being made in relation to the speaker's professional integrity. The question to be answered was whether or not it was appropriate for Astra to have sponsored the meeting.

The Appeal Board noted the previous case (Case AUTH/270/2/95) referred to by both Astra and the Panel. In the Appeal Board's view the circumstances of that case were different to the cases now before it. Each case should be considered on its own facts.

The Appeal Board noted that Astra had asked the speaker to talk about asthma in general to a group of doctors and asthma nurses. The talk had to be relevant to the audience. The Appeal Board noted that high dose inhaled steroids were referred to in the BTS Guidelines for the treatment both of asthma in children under 5 and adults and school children. In addition, the Appeal Board noted that according to prescription data the use of high dose inhaled steroids was not uncommon in children and so the Appeal Board considered that any problems associated with such use would be of interest to the audience.

The Appeal Board noted the submission that the problems associated with the use of high doses of inhaled steroids in children had not formed a major part of the presentation. The talk had been divided into four parts of which growth retardation in children on high doses of inhaled steroids was one. The Appeal Board noted that the speaker had published a paper in The Lancet on the use of high doses of fluticasone in six severely asthmatic children and considered that it would have been odd if he had not referred to his work when addressing an audience which would have practical experience of the

use of high dose inhaled steroids in children. The Appeal Board noted that, before addressing the issues surrounding the use of high dose inhaled steroids, the speaker was careful to establish with the audience the usual doses of inhaled steroids in children and to emphasise that the doses of steroids he was about to discuss were unlicensed. The Appeal Board noted the submission that following his talk he had been closely questioned on the subject by some members of the audience.

The Appeal Board considered that the content of the talk was not unbalanced. The references to the use of high dose inhaled steroids in children had been only part of the presentation. The use of high doses of inhaled steroids in children was not uncommon and would have been directly relevant to the audience. The Appeal Board therefore ruled no breach of Clause 7.2 of the Code. The Appeal Board did not consider that the content of the meeting had disparaged fluticasone and ruled no breach of Clause 8.1 of the Code. These rulings applied to both cases.

The appeal was therefore successful.

Complaints received **19 May 1997**

Cases completed **15 October 1997**

CASE AUTH/572/6/97 *NO BREACH OF THE CODE*

DOCTOR v PHARMACIA & UPJOHN

Article in Daily Mail about Caverject

A doctor alleged that an article in the Daily Mail promoted Caverject, Pharmacia & Upjohn's product for treating erectile dysfunction. The complainant also alleged that The Impotence Association, which was mentioned in the article, was financed by Pharmacia & Upjohn and accordingly it actively promoted Caverject.

The Panel noted that neither Pharmacia & Upjohn nor its public relations consultants had provided written information or briefing to the Daily Mail. In response to a request from the journalist who wrote the article, the public relations consultants had made contact with some physicians to identify patients who had received treatment for erectile dysfunction but at no time were either the company or the public relations consultants aware of the specific type of treatment received by the patients. No breach of the Code was ruled. The Panel did not accept the allegation that The Impotence Association promoted the use of Caverject to the public. No breach of the Code was ruled. The rulings were upheld by the Appeal Board on appeal from the complainant.

A doctor complained about a one page feature on male impotence which appeared in the Daily Mail on 17 June 1997. The page was headed "Can this pill beat the great male taboo?" and although the following article referred mainly to an oral medicine which was being developed for the treatment of impotence, the last section referred to one patient's use of Caverject, an injectable product marketed by Pharmacia & Upjohn Limited for the treatment and diagnosis of erectile dysfunction. A sub-article on the same page entitled "Impotence made me feel less of a man" told a more detailed story of a patient who used Caverject. The feature page ended with the name and telephone number of The Impotence Association Helpline.

COMPLAINT

The complainant alleged that the article was a promotional piece using the name Caverject, a prescription only medicine. The complainant alleged that such direct promotion to the public contravened the Code.

The article gave information about The Impotence Association Helpline. The complainant said that The Impotence Association was financed by Pharmacia & Upjohn and accordingly it actively promoted the use of Caverject.

RESPONSE

Pharmacia & Upjohn stated that the article in question was not promotional as neither Pharmacia & Upjohn nor its agent was responsible for its production. The article was written by a journalist with no relationship to Pharmacia & Upjohn. The company noted that the article mentioned Caverject by name only in direct quotes from interviewed patients who had been prescribed this therapy. The company understood that the journalist originally contacted The Impotence Association which, to protect the confidentiality of its patient contacts, directed the journalist to various sources, including Pharmacia & Upjohn's public relations consultants. In response to a request for help in locating patients suffering from erectile dysfunction the public relations consultants made contact with a number of known physicians with a brief to contact patients who had received treatment for erectile dysfunction and who were willing to be interviewed and photographed by the Daily Mail. These physicians used many treatments including drug therapy, medicinal and vacuum devices and the request for patients did not allude to a particular therapy.

The physicians then approached their patients to establish if they would be willing to take part. Those that were willing were phoned by the public relations consultants to ensure that they clearly understood that the Daily Mail wished to photograph them and interview both themselves and their partners on the problems that they had encountered suffering from erectile dysfunction. Direct contact between the patient and the Daily Mail was then established.

At no point was Pharmacia & Upjohn or its public relations consultants aware of the specific type of

treatment received by the patients being interviewed. The interviews took place directly between the journalist and the patient. Neither Pharmacia & Upjohn nor its public relations consultants provided any written information or briefing to the Daily Mail.

Pharmacia & Upjohn submitted that The Impotence Association was a charitable organisation originally set up to provide support and information to patients with impotence problems. It was originally funded by Upjohn Ltd and achieved charitable status in 1996. The Impotence Association had always been and remained autonomous in its activities and its purpose was to provide balanced and holistic information about impotence. Pharmacia & Upjohn had no control over the structure, management or running of the Association. The Impotence Association was run by the trustees of the Association who enjoyed a reputation of some standing. Two of the trustees were world leaders in the treatment of impotence. The third trustee was a well-known counsellor in sexual and marital problems who also wrote extensively on these subjects.

Pharmacia & Upjohn understood that The Impotence Association now received funding and charitable donations from a number of sources including Pharmacia & Upjohn. The Impotence Association did not promote the use of any particular treatment including Caverject. The Impotence Association did provide two leaflets and background information on The Impotence Association. Copies of the leaflets were supplied.

Pharmacia & Upjohn stated that no press release or any other information was provided to the Daily Mail with regard to this article. The company had no influence on the activities of The Impotence Association Helpline. The company did support the printing and distribution of the two information leaflets previously referred to, these being "It Takes Two: A Couples Guide to Erectile Dysfunction" and "Would a woman recognise the signs?" These leaflets, as well as other material, were provided by The Impotence Association to enquirers. Pharmacia & Upjohn submitted that it did not provide The Impotence Association with material relating to Caverject. The Impotence Association did not provide information relating to Caverject to enquirers.

Pharmacia & Upjohn pointed out that the article referred twice to injectable therapy as "...a miserable prelude to love making..", but did however refer positively to several unlicensed products by brand name.

PANEL RULING

The Panel noted that neither Pharmacia & Upjohn nor its public relations consultants had provided written information or briefing to the Daily Mail. The public relations consultants had made contact with some physicians to identify patients who had received treatment for erectile dysfunction and were willing to be photographed. At no time were either Pharmacia & Upjohn or its public relations consultants aware of the specific type of treatment received by the patients being interviewed.

The Panel noted that the Daily Mail article mentioned Caverject by name but this was not necessarily in breach of the Code. The article referred to two patients who had used Caverject and their comments were not unreasonable.

In the Panel's view the article was not an advertisement for a prescription only medicine as prohibited by Clause 20.1 of the Code. The role of the company and its public relations consultants was not unacceptable given the requirements of Clause 20.2 of the Code. The company's public relations consultants had co-operated in identifying patients for interview and it was possible that some of these would have been prescribed Caverject but this had not been a requirement. In the absence of any further evidence as to what the company had said to the Daily Mail, the Panel ruled that there was no breach of either Clause 20.1 or Clause 20.2 of the Code.

The Panel noted the relationship between The Impotence Association and Pharmacia & Upjohn. It was not necessarily unacceptable for pharmaceutical companies to give money to patient groups, charities, etc. This would depend on how the money was used and the role of the sponsoring company in relation to the activities of the organisations. Each instance would have to be judged on its merits. Companies were more likely to support charities which were relevant to their interests. The Impotence Association had been originally funded by Upjohn but now received funding from a number of sources including Pharmacia & Upjohn. The Panel noted that the leaflets referred to treatments in general. The leaflet "Would a woman recognise the signs?" stated that general practitioners may be able to offer a full range of treatments or may refer to a specialist. It also stated that it was possible to treat up to 95% of impotent men. The leaflet "It Takes Two" gave more information about treatment options. Injection therapy was included along with other treatments. The Panel noted that there had not been a specific complaint about the leaflets. The Panel noted the submission that Pharmacia & Upjohn did not provide The Impotence Association with material relating to Caverject and nor did The Impotence Association provide information about Caverject to enquirers. In the circumstances the Panel did not accept the allegation that The Impotence Association promoted the use of Caverject to the public. No breach of Clause 20.1 or Clause 20.2 was ruled.

APPEAL BY THE COMPLAINANT

The complainant said that Pharmacia & Upjohn asserted that "the article in question published in the Daily Mail is not promotional as neither Pharmacia & Upjohn or our agent are responsible for its production". This statement was clearly incorrect as the letter then went on to detail the involvement of The Impotence Association (partly financed by Pharmacia & Upjohn) and the direct involvement of its public relations consultants.

The Impotence Association directed the journalist to contact the public relations consultants which in turn arranged for the journalist to contact named patients. Whilst Pharmacia & Upjohn vainly asserted that "at no time was [the public relations consultants] aware of the specific type of treatment received by the patients being interviewed", it was an extraordinary coincidence that the only two patients both named and photographed in the article were treated with Caverject. The complainant did not accept that it was coincidence.

The complainant contended therefore that there was

collusion between the public relations consultants acting as agent for Pharmacia & Upjohn, and the Daily Mail journalist to ensure that Caverject was effectively promoted.

Accordingly, the complainant appealed against the Panel's ruling in respect of Clause 20.2 in that the information provided in this promotion was not presented in a balanced way and was misleading with respect to the safety of the product (no mention being made of the adverse reactions) and could encourage members of the public to ask their doctors to prescribe a specific medicine.

RESPONSE FROM PHARMACIA & UPJOHN

Pharmacia & Upjohn said that it noticed that the main point for the appeal was the disbelief that neither Pharmacia & Upjohn nor its public relations consultants were aware of the specific type of treatment received by the patients being interviewed. Pharmacia & Upjohn was surprised to read the suggestion that there was "collusion between [the public relations consultants], acting as agent for Pharmacia & Upjohn, and the Daily Mail journalist to ensure that Caverject was effectively promoted". This was clearly not the case as previously outlined by the company.

FURTHER COMMENTS FROM THE COMPLAINANT

Although invited to do so, the complainant did not comment upon Pharmacia & Upjohn's response to the appeal.

APPEAL BOARD RULING

The Appeal Board considered that there was no evidence to support the allegation that Pharmacia & Upjohn or its agent were responsible for the article in question or were aware of the specific type of treatment received by patients who were interviewed for the article. The Appeal Board therefore upheld the Panel's ruling that there had been no breach of the Code.

The appeal therefore failed.

Complaint received **23 June 1997**

Case completed **15 October 1997**

CASE AUTH/574/6/97

E MERCK v LEO

Curatoderm detail aid

E Merck made a number of allegations in relation to a detail aid entitled "Dovonex versus tacalcitol" which had been issued by Leo. Merck marketed Curatoderm (tacalcitol).

The Panel ruled a breach of the Code in relation to a reference to once daily use of Dovonex in a cost comparison chart. Dovonex was licensed for twice daily use. A claim that tacalcitol could not be used for long term use was ruled in breach as the SPC for Curatoderm did not prohibit long term use, though it made clear that this would not be a normal occurrence. Similarly ruled in breach were two statements that use of tacalcitol was normally limited to two eight week periods per year as the licence had been varied to refer to periods of twelve weeks.

A statement "Limited comparative data available" in a box headed "tacalcitol" was ruled by the Panel not to be in breach on the basis of the evidence before it. The Code permitted critical references to other products provided that these were fair and could be substantiated. On appeal by Merck, the Appeal Board considered that the use of the word "limited" was denigrating and that it hinted at inadequacy. It gave the impression that there was not sufficient data to assess the product. The Appeal Board considered the statement disparaging of tacalcitol and ruled it in breach.

A statement comparing calcaemic potential of first and second generation vitamin D analogues was considered to be misleading because it implied that Dovonex was 100 to 200 times less calcaemic than tacalcitol and calcitriol and this was not so. Further, it was not sufficiently clear that the data referred to animal studies and the clinical relevance was not apparent. A breach was also ruled because there had been a failure to comply with a previous undertaking. Leo had amended the earlier material but the amendment had not been adequate.

A claim for the superior efficacy of Dovonex versus topical steroids was ruled in breach because only one topical steroid had been studied in the quoted references and not more than one as would be assumed. A breach was also ruled because of the failure to provide references when referring to published clinical data.

No breach was ruled in relation to an allegation concerning a cost comparison as the Panel considered that the claim would be taken to mean that on a gram for gram basis Dovonex 120g was less expensive than other pack sizes. The Panel did not consider that the claim included any implication of cost-efficacy.

E Merck Pharmaceuticals complained about a Dovonex detail aid (ref 1327 date of preparation: July 1996) issued by Leo Pharmaceuticals. The detail aid had been used at an exhibition on 7 May 1997 and was entitled "Dovonex versus tacalcitol - the evidence". The detail aid was withdrawn from use in June 1997. Merck marketed Curatoderm (tacalcitol) and the company made a number of allegations.

A BAR CHART ON PAGE 1 ENTITLED "RELATIVE COST OF VITAMIN D TREATMENTS FOR PSORIASIS".

The bar chart had two horizontal bars one of which was vertically divided into two along its length. The first half of the bar represented the cost of once daily treatment with Dovonex and included a label, in red, "Dovonex od". The second half of the bar represented the cost of twice daily treatment with Dovonex. The other bar represented the cost of once daily treatment with tacalcitol.

1 Once daily Dovonex

COMPLAINT

Merck stated that Dovonex was not approved for once daily use as indicated by "Dovonex od". The presentation of the cost of treatment for once daily use as a comparison with the cost of tacalcitol treatment was clearly promoting the use of the product outside the licensed dosage recommendation. A breach of Clause 3.2 of the Code was alleged.

RESPONSE

Leo stated that the detail aid clearly and boldly recommended the use of Dovonex twice daily. This recommendation was made at least once on every page and twice on page 1. Data were presented which demonstrated loss of efficacy when Dovonex was used once daily. This was highlighted on page 1 which included the statement "Dovonex twice daily is significantly more effective than Dovonex once daily (change in PASI [Psoriasis Area and Severity Index], $p < 0.001$)." This was a clear statement of the message throughout, which recommended twice daily application. There was no promotional claim or recommendation anywhere in the detail aid that Dovonex should be prescribed once daily, and there was a clear intention to promote the use of Dovonex according to the licensed dose recommendation. There was no ambiguity and no breach of Clause 3.2.

PANEL RULING

The Panel noted that the cost comparison bar chart was entitled "Relative cost of vitamin D treatments for psoriasis" and included a bar, half of which was labelled with "Dovonex od" (in red) and the cost of such treatment. The Panel considered that many readers might assume that Dovonex could be used once daily and was one of the vitamin D treatments referred to in the title of the chart. This impression was further endorsed by the inclusion of the cost of once daily Dovonex treatment. The Panel noted that Dovonex was only licensed for twice daily use. The Panel considered that the reference to once daily Dovonex in a cost comparison chart amounted to promotion of that dose which was not in accordance with its product licence. A breach of Clause 3.2 of the Code was ruled as alleged.

The Panel noted that page 1 included an efficacy

comparison between Dovonex once daily, Dovonex twice daily and tacalcitol. Although there was no allegation about this section, the Panel considered that this also amounted to promotion of a dose not in accordance with the product licence as above. The Panel requested that its concerns be drawn to Leo's attention.

2 Claim: "Unlike tacalcitol, Dovonex can be used for long-term treatment...."

COMPLAINT

Merck stated that the claim was untrue. The Curatoderm summary of product characteristics (SPC) stated, in the section headed "Dosage and method of administration", "Adults and the Elderly: Apply sparingly, once daily to the affected areas, preferably at bedtime. The amount applied should not exceed 5g of ointment/day. Normally duration of treatment depends on the severity of the lesions and should be decided by the physician. Experience shows that treatment will not usually need to exceed 2 periods of 12 weeks each year." Merck stated that this clearly did not exclude long term treatment with tacalcitol. A breach of Clause 7.2 was alleged.

RESPONSE

Leo submitted that psoriasis was a chronic, lifelong skin disease where most patients required treatment for greater than two periods of 12 weeks per year. Indeed, published data showed that up to 60% of patients required continuous treatment with no interruption.

There was no time limitation on the use of Dovonex and the claim referring to long-term treatment could be fully substantiated by the given reference, and others. The promotion of tacalcitol for continuous use was limited by the statement that "treatment will not usually need to exceed two periods of 12 weeks each year".

In view of the restrictions within the Curatoderm product licence, it was not clear to Leo how Clause 7.2 could have been breached.

PANEL RULING

The Panel noted that the Curatoderm SPC stated that "Normally duration of treatment depends on the severity of the lesions and should be decided by the physician. Experience shows that treatment will not usually need to exceed two periods of 12 weeks each year." The SPC did not say that treatment must not exceed two periods of 12 weeks each year. In the Panel's view the SPC did not prohibit long-term treatment with tacalcitol although it made it clear that this would not be a normal occurrence. The Panel considered that the claim "Unlike tacalcitol, Dovonex can be used for long-term treatment...." was misleading and ruled a breach of Clause 7.2 of the Code.

B BOX ON PAGE 2 HEADED "TACALCITOL".

The box contained the statement "Treatment usually limited to no more than two courses of eight weeks each year" below which was the diagram of a calendar with two eight week periods highlighted by red arrows. Below the calendar was a second statement "Limited comparative data available".

3 "Treatment usually limited to no more than two courses of eight weeks each year."

COMPLAINT

Merck said that at the time of use of this promotional material this was not a restriction which applied to tacalcitol and referred to the information in the SPC regarding the twelve week period which had been referred to in point 2 above. A breach of Clause 7.2 was alleged.

RESPONSE

Leo said that this statement was true at the time of approval and was consistent with the latest published data sheet (Ref ABPI Compendium 1996-7). The modification to the Curatoderm SPC first appeared in MIMS in March 1997. Leo accepted that this was an unfortunate error and had so informed Merck, in writing. Leo considered it somewhat disingenuous of Merck to subsequently allege a breach of the Code. It did the reputation of the industry no good if companies rushed in with complaints every time minor adjustments were made in prescribing information. It might have been more appropriate for Merck to have informed Leo of this licence modification.

PANEL RULING

In response to a request for further information from the Authority, Merck said that there had been a change in the dosage wording from a reference to a period of eight weeks, to twelve weeks. The variation approval was received on 3 August 1996 and revised SPCs were used subsequent to that date. The change was reflected for the first time in MIMS, March 1997. Merck did not issue any specific mailings to doctors or pharmacists at the time of the revision.

The Panel noted that the tacalcitol licence variation which extended the usual treatment period from eight to twelve weeks was granted in August 1996 and details were published in MIMS in March 1997. The detail aid in question was prepared in July 1996 and was still in use in May 1997. The Panel noted that Leo had acknowledged that the licence had been changed. The Panel considered that companies featuring various aspects of competitor products in promotional material were at risk of having to withdraw that material forthwith should details of those products change. In this case the continued use of an inaccurate reference to the fact that treatment with tacalcitol was usually limited to no more than two courses each of eight weeks was in breach of Clause 7.2 of the Code and the Panel ruled accordingly.

4 "Limited comparative data available".

COMPLAINT

Merck alleged that this was a disparaging reference which was not substantiated in breach of Clause 8.1. Merck noted that in the same detail aid a claim that for Dovonex

there was a "wealth of published data" was apparently four references.

RESPONSE

Leo submitted that Dovonex was supported by a wealth of published comparative clinical trials against all of the commonly used treatments, examples of which were clearly referenced. To date Dovonex had been the subject of many comparative studies. By way of contrast the Curatoderm Scientific Brochure, in current use, contained no references to randomised, controlled, active comparator clinical trials. Furthermore, the most recent review of the treatment of psoriasis from the Drug and Therapeutics Bulletin also supported the statement "Limited comparative data available". Copies of the brochure and the Drug and Therapeutic Bulletin were provided.

Leo said that the statement could not therefore be considered disparaging and there was no breach of Clause 8.1.

PANEL RULING

The Panel noted that it was acceptable for companies to make adverse comments about competitor products providing such critical references were accurate, balanced, fair and could be substantiated. This was reflected in the supplementary information to Clause 8.1 of the Code.

The Panel noted that the Curatoderm Scientific Brochure was dated December 1995 and the Drug and Therapeutics Bulletin was dated March 1996. With reference to tacalcitol the Drug and Therapeutics Bulletin contained the statement "As yet no randomised, controlled trial data have been published". It was possible that a number of papers on tacalcitol could have been published since the Drug and Therapeutics Bulletin had been issued. In the absence of any evidence from Merck that this was so the Panel ruled no breach of Clause 8.1 of the Code.

APPEAL BY MERCK

Merck said that it considered the ruling of the Panel to be incorrect and not based on an evaluation of all the information available.

The Leo statement "tacalcitol ... Limited comparative data available" was incorrect. It was a "disparaging reference" as it was not accurate, balanced, fair or capable of substantiation. This was true at the time the promotional item was printed and certainly at the time it was known to be used, May 1997.

The reasons and evidence that the Leo statement was in breach of the Code were as follows:

1 Curatoderm (tacalcitol ointment) was approved by the UK authorities as a medicinal product and therefore, by definition, there were satisfactory data available on safety and efficacy. The statement "Limited comparative data" suggested that the quality of data available was less than that required for the issue of a valid marketing authorization.

2 The Leo response to the complaint stated that the Curatoderm Scientific Brochure contained no references to randomised, controlled active comparator clinical trials. The detail aid statement referred only to "comparative data" and it was this statement which must be tested against the evidence and which must be substantiated. It was not acceptable to attempt to redefine the meaning of such a statement at a later date.

Merck referred to seven papers which included controlled trials comparing tacalcitol ointment (Curatoderm) against placebo, betamethasone valerate ointment, calcipotriol ointment and dithranol. The company submitted that it was clear that these were "comparative data" within any reasonable definition as applied to clinical trials, all of which had been made available by its medical information department and would have been available to Leo at the time of the use of the detail aid.

The statement made by Leo "tacalcitol ... Limited comparative data available" was not accurate, balanced or fair and was not substantiated by the data. The statement was disparaging and in breach of Clause 8.1.

RESPONSE FROM LEO

Leo said that the detail aid in question made the following two claims on the second page. Firstly that for tacalcitol there was limited comparative data available and secondly that for Dovonex there was "a wealth of published data showing the superior efficacy of Dovonex Ointment vs tars, dithranol and topical steroids".

It was important to be clear what was meant by comparative data. From the above statements in the detail aid, comparative data clearly referred to comparison with other available products. Data in comparison with inactive vehicle treatment was not for consideration in this matter.

Dovonex was the most extensively investigated topical anti-psoriatic treatment available in the UK when judged by the high standards and number of randomised controlled trials.

A table of the available comparative data in respect of tacalcitol was provided (a total of 8 papers) together with similar data for Dovonex (a total of 35).

Leo said that it must be concluded that the statements included in the Dovonex detail aid were a fair reflection of the facts. No disparaging statements were made in respect of the absolute efficacy or safety or any other aspect of tacalcitol, and there was no breach of Clause 8.1.

FURTHER COMMENTS FROM MERCK

Merck said that the appeal related solely to the statement made by Leo "tacalcitol ... Limited comparative data available" which appeared within a box separate from other statements. It was not a comparative, but an absolute statement. This clearly attempted to suggest that less than acceptable data were available for tacalcitol (despite the product being approved by the UK regulatory authority). This statement regarding tacalcitol was not supported by the data.

Merck pointed out that the table of comparative data for Dovonex which Leo had now produced to try to support its statement, included a number of studies with Dovonex which were outside its own definition of comparative

data. According to Leo, comparative data clearly referred to "comparison with other available products" and this would not, for example, cover its eight studies using combinations with PUVA/UVA or UVB.

There was no definition or understanding of the term "comparative data" which excluded placebo controlled studies as Leo tried to indicate. These types of studies were of course considered to be essential to demonstrate the efficacy of new products.

The reference to the Drug and Therapeutics Bulletin in Leo's original response as support for its statement was of no relevance as data on tacalcitol was available at the time the Drug and Therapeutics Bulletin was published. Presumably Leo was asked to comment on the draft by the publishers, but Merck was not contacted. It was therefore not an up-to-date evaluation of the evidence at the time of publication of the article or the detail aid.

Merck stated that it was also untrue that the relevant page of the detail aid made only two claims. Apart from the claim for the safety and efficacy of Dovonex there were also the untrue claims for the duration of the treatment with tacalcitol and the statement concerning the calcaemic effect of tacalcitol.

This statement made by Leo in the detail aid concerning tacalcitol was not comparative to Dovonex. It was not accurate, balanced, fair or based on an up-to-date evaluation of the evidence. It was, and presumably was intended to be, a disparaging reference to tacalcitol, and was in breach of Code 8.1 of the Code.

APPEAL BOARD RULING

The Appeal Board considered that a study comparing a product with placebo was technically a comparative study although health professionals, the intended audience, would think that "comparative data" was a reference to comparisons with active products and not with placebo.

The Appeal Board considered that the use of the word "limited" was denigrating and hinted at inadequacy. It gave the impression that there was not sufficient data to assess the product. The Appeal Board considered that the statement "Limited comparative data" was disparaging of tacalcitol and ruled a breach of Clause 8.1 of the Code.

The appeal on this point was therefore successful.

C CHART ON PAGE 2 DEPICTING THE HISTORY OF VITAMIN D ANALOGUES.

The vertical chart showed the research and development history of vitamin D analogues for psoriasis treatment which, according to the chart, began in 1970 with the synthesis of calcitriol which had an "Undesirable pharmacological profile". The chart referred to 1974 and the identification of tacalcitol which had "Similar calcaemic properties to calcitriol". These two products came under a heading of "first generation". Under a heading of "second generation" the entry for 1985 stated ".... calcipotriol synthesised. Pre-clinical studies show 100 to 200 times less calcaemic than first generation".

5 Statement comparing calcaemic potential of first and second generation vitamin D analogues.

COMPLAINT

Merck said that this chart directly implied that tacalcitol was a "first generation" product and that pre-clinical studies had shown Dovonex to be 100 to 200 times less calcaemic than such products.

Merck said that this claim was based solely on one limited study in animals. It was not relevant to the clinical use of tacalcitol and it did not reflect either the dosage or warning sections of the SPCs for tacalcitol and calcipotriol.

The claim directly contravened the undertaking given by Leo in case AUTH/410/3/96 where the same claims had been made. Case AUTH/410/3/96 had been completed in March 1996 but the detail aid in question was dated July 1996. Leo had therefore continued to make statements which they had undertaken not to use in the future. Breaches of Clause 7.2 and 21 were alleged.

RESPONSE

Leo noted that Merck did not challenge the factual accuracy of the data as presented.

Leo noted the reference made to Case AUTH/410/3/96. It was entirely appropriate to discuss in promotional material risks associated with treatment. The most serious risk in using any vitamin D analogue was the risk of hypercalcaemia, a risk noted in the SPCs for such products whether given orally or topically.

Leo said that given the ruling in Case AUTH/410/3/96 its presentation of the facts regarding calcaemic potential was modified to remove any suggestion that these data referred to clinical effect or implied clinical comparison. Hence use of the phrases "synthesised in the laboratory" and "Pre-clinical studies show....." plus the graphic separation of first generation and second generation products. Leo submitted that in the absence of any 'clinical data' on relative calcaemic potential, the pre-clinical data must be considered relevant.

Leo said that the data were clearly presented and there was no breach of Clause 7.2 or 21.

PANEL RULING

The Panel noted that in Case AUTH/410/3/96 the statement "Pharmacologically tacalcitol is 50 to 100 times more calcaemic than Dovonex" had appeared in a press release. The Panel had considered that the comparison of the calcaemic potential of the two products was too brief. It had not been qualified or put into context and it had not been made obvious that the statement was derived from animal data. The clinical relevance of the statement was not apparent. The Panel noted that both Dovonex and tacalcitol were contraindicated in patients with known disorders of calcium metabolism and that both could precipitate hypercalcaemia in certain patient groups. The Panel had accepted that tacalcitol was more calcaemic than Dovonex but considered that the difference in strength and dosage of the two products would erode this difference. In any case the clinical significance of the difference in calcaemic potential between the two products was not clear. A breach of Clause 7.2 of the Code had been ruled and this had been accepted by Leo.

The Panel noted in this case that the comparison of the calcaemic potential of Dovonex was a more general one with first generation vitamin D analogues as a whole as opposed to with tacalcitol specifically. The Panel noted that Case AUTH/410/3/96 referred to tacalcitol being 50 to 100 times more calcaemic than Dovonex. In the Panel's view the statement in the case now before it with respect to calcipotriol (Dovonex) that "Pre-clinical studies show 100 to 200 times less calcaemic than first generation" was misleading. The use of the reference to first generation Vitamin D analogues implied that Dovonex was 100-200 times less calcaemic than both tacalcitol and calcitriol and this was not so. Further it was not sufficiently clear that the data referred to animal studies and the clinical relevance was not apparent. The Panel noted that the comments made in Case AUTH/410/3/96 would also apply to the case now before it. The Panel ruled a breach of Clause 7.2.

The Panel noted that a comparative statement regarding the calcaemic potential of Dovonex versus tacalcitol had previously been ruled to be in breach of the Code. The Panel considered that although the exact statement had not been used as such, the section in the detail aid represented a failure to comply with a previous undertaking to avoid similar breaches of the Code in the future. A breach of Clause 21 of the Code was ruled.

The Panel noted that in previous cases ruled in breach of Clause 21 of the Code the Panel had also ruled a breach of Clause 2 of the Code. The Panel noted that a breach of Clause 2 of the Code had not been alleged. This case was different to previous cases which had concerned the continued use of material ruled in breach whereas in the case now before the Panel the company had amended the material but the amendment had not been adequate.

D BOX ON PAGE 2 HEADED "DOVONEX [CALCIPOTRIOL]"

Immediately below the heading was the claim "Long-term continuous efficacy" and a diagram of a calendar with a double ended red arrow across all twelve months. Facsimiles of journal titles appeared below the calendar followed by the claim "Wealth of published data Shows the superior efficacy of Dovonex Ointment versus tars, dithranol and topical steroids". One reference was given to support each efficacy claim of Dovonex versus tars and Dovonex versus dithranol. Two references were given to support the efficacy claim of Dovonex versus topical steroids (Kragballe *et al* 1991 and Cunliffe *et al* 1992).

6 Claim for superior efficacy of Dovonex versus topical steroids

COMPLAINT

Merck pointed out that the abstracted results of the Cunliffe paper stated that "....there were no significant between treatment differences". This reference also stated that "calcipotriol produced significantly more local side effects.....". Merck contended that the use of this reference was misleading and inaccurate when used to support the claim made concerning "superior efficacy". A breach of Clause 7.2 was alleged.

RESPONSE

Leo contended that Merck was highly selective with its quote from the Cunliffe paper. Cunliffe *et al* also stated that "Analysis of patient assessment at six weeks showed clearance or marked improvement in 61.2% of the calcipotriol patients and 50.5% with betamethasone (95% CI 1.4 to 20.8)". In the Kragballe paper the significantly superior clinical efficacy of Dovonex Ointment compared to betamethasone was evident for all the main outcome measures ie PASI, individual components of PASI and patients' assessment of response.

Leo submitted that the claim was substantiated by the references given. Further published data were available to substantiate the claim of superior efficacy of Dovonex Ointment relative to steroids and there was no breach of Clause 7.2.

PANEL RULING

The Panel noted that the section included the claim "Long-term continuous efficacy". The Panel considered that it was not unreasonable to assume that the references cited to support the superior efficacy claims involved long-term treatment. The Panel noted that the papers by Cunliffe *et al* and Kragballe *et al* were only six week studies. In addition the Panel noted that both the Cunliffe study and that by Kragballe *et al* were comparisons of Dovonex versus betamethasone. The Panel noted that although Cunliffe *et al* had shown no difference between Dovonex and betamethasone in terms of PASI, patient assessment had shown a significant difference in favour of Dovonex. The Kragballe paper stated that "....calcipotriol ointment (Dovonex) was superior to betamethasone valerate ointment in psoriasis vulgaris". The Panel considered that there was, therefore, evidence to substantiate the superiority of Dovonex versus betamethasone.

The Panel considered that the claim "Shows the superior efficacy of Dovonex Ointment versus... topical steroids" followed by two reference numbers would be taken by most readers to imply that more than one topical steroid had been studied in the quoted references and this was not so. The Panel considered that the statement at issue was misleading and ruled a breach of Clause 7.2 of the Code.

E DOVONEX SUMMARY PAGE 3

7 Reference to published trials

COMPLAINT

Merck alleged a breach of Clause 7.5 of the Code as the statement "Published clinical data shows...." was not referenced.

RESPONSE

Leo said that this statement referred to the wealth of data in general, not to one or more specific studies, and was consistent with the licensed indication. References were not, therefore, required, the statement could be substantiated and there was no breach of Clause 7.5.

PANEL RULING

The Panel noted that Clause 7.5 of the Code stated that "When promotional material refers to published studies, clear references must be given". The Panel considered that the statement "Published clinical data shows...." did refer to published studies but noted that no references had been given. A breach of Clause 7.5 of the Code was ruled.

In consideration of this matter the Panel noted that Clause 7.5 applied to references to published studies in promotional material. This might include those which referred to licensed indications. The exemption in Clause 7.4 of the Code that substantiation need not be provided in relation to the validity of indications approved in the marketing authorization did not apply to Clause 7.5.

8 Reference to two 8 week treatment courses with tacalcitol.

COMPLAINT

Merck alleged that the statement "Continuous treatment is not possible with tacalcitol since treatment is usually limited to no more than 2 courses of 8 weeks duration each year" was not true. At the time of use of this promotional material this statement was not an up-to-date or accurate reflection of any restrictions which applied to the use of tacalcitol. Merck referred to the extract from the tacalcitol SPC as quoted in point 2 above.

RESPONSE

Leo referred to its response to point number 3 as above.

PANEL RULING

The Panel considered that its ruling in point 3 above also applied to this matter. A breach of Clause 7.2 of the Code was ruled.

9 Statement "Prescribe Dovonex as 120g Ointment or Cream for economic long-term treatment"

COMPLAINT

Merck alleged a breach of Clause 7.2 of the Code as this statement was not substantiated and made a claim regarding the economic evaluation of a medicine.

RESPONSE

Leo noted that this statement was made under a photograph of the range of available pack sizes of Dovonex. The relative NHS costs of Dovonex Ointment and Cream packs were as follows:

Dovonex 120g	£29.40	£/g - 0.245
Dovonex 60g	£16.30	£/g - 0.272
Dovonex 30g	£8.15	£/g - 0.272

Dovonex 120g Cream and Ointment was less expensive per gram than Dovonex 30g/60g Cream and Ointment and the statement was justified by relative cost saving by prescription of the larger pack size.

Leo said that there was no breach of Clause 7.2.

PANEL RULING

The Panel noted that the claim "Prescribe Dovonex as 120g Ointment or Cream for economic long-term treatment" appeared under a photograph of the range of Dovonex Cream and Ointment packs - 30g/60g/120g. Above the photograph was the statement "Dovonex is available in a wide range of presentations". The Panel considered that given the context the claim in question would be taken to mean that on a gram for gram basis Dovonex 120g was less expensive than the other pack sizes. The Panel did not consider that the claim included any implication of cost-efficacy. No breach of the Code was ruled.

Complaint received **23 June 1997**

Case completed **7 November 1997**

CASE AUTH/575/7/97

UCB PHARMA v SCHERING-PLOUGH

Clarityn advertisements

UCB Pharma complained about two advertisements for Clarityn issued by Schering-Plough.

One took the form of an advertisement feature and included the statement "When symptoms are very severe antihistamines can be co-prescribed with topical corticosteroids, such as mometasone furoate aqueous nasal spray". UCB alleged that the prescribing information for Schering-Plough's product Nasonex (mometasone furoate) should therefore have been included as well as that for Clarityn. A breach of the Code was ruled.

A statement referring to the possible interaction of certain antihistamines, such as cetirizine (UCB's product Zirtek), with alcohol, potentiating its adverse effect on cognitive behaviour and psychomotor function and affecting driving, was considered not to accurately reflect the data regarding cetirizine, alcohol and driving and was ruled in breach. Upon appeal by both parties the Appeal Board confirmed that ruling and ruled the statement to be also in breach because it disparaged cetirizine.

The other advertisement referred to Clarityn as the world's leading antihistamine. The Panel did not consider that this would be interpreted as meaning the most popular globally in terms of prescription and over-the-counter sales as Schering-Plough contended. Its meaning was not clear. It could be taken to mean that it sold more doses or that it was regarded as being the best product. The Panel considered that a special merit had been claimed which could not be substantiated and a breach was ruled.

UCB Pharma Limited complained about two advertisements for Clarityn (loratadine) issued by Schering-Plough Ltd. UCB Pharma marketed Zirtek (cetirizine).

A ADVERTISEMENT FEATURE

A full page advertisement headed "Advertisement Feature" appeared in GP (23 May 1997), Pulse (30 May 1997) and Doctor (19 June 1997). The advertisement, entitled "Holiday Medicine:", had the general appearance of editorial material and gave detailed information about the use of antihistamines by patients who might go overseas and unwittingly break local laws regarding driving and medicines. The advertisement gave information on sedation as a possible side-effect of antihistamines and also their possible interaction with alcohol. The advertisement included the prescribing information for Clarityn.

1 "When symptoms are very severe antihistamines can be co-prescribed with topical corticosteroids, such as mometasone furoate aqueous nasal spray."

COMPLAINT

UCB alleged that this statement was clearly promoting Schering-Plough's Nasonex and as no prescribing information had been provided it was in breach of Clause 4 of the Code. In correspondence with UCB (dated 30 May 1997), Schering-Plough had stated "In future editions we will amend the [advertisement] to include Nasonex prescribing information, although this will take a few weeks ..." UCB pointed out that despite this undertaking from Schering-Plough, the advertisement was reissued in the 19 June issue of Doctor. UCB considered that Schering-Plough would have had ample opportunity to remove the advertisement given its expressed concern on this point.

RESPONSE

Schering-Plough submitted that it was not sure it was correct in not including prescribing information for Nasonex (mometasone furoate) and in future issues of the advertisement it would have amended it to include this (allowing for time to change plates etc). In view of this complaint, Schering-Plough had decided not to publish the advertisement again until the Panel had reached a conclusion on all of UCB's complaints. Appropriate action would be taken at that stage.

PANEL RULING

The Panel considered that the reference to mometasone furoate aqueous nasal spray (Schering-Plough's product Nasonex) in the advertisement meant that prescribing information was required. The advertisement promoted mometasone furoate. No prescribing information for Nasonex had been included in the advertisement. The Panel therefore ruled a breach of Clause 4.1 of the Code.

2 "Certain antihistamines, such as cetirizine, may interact with alcohol, potentiating its adverse effect on cognitive ability and psychomotor function. A person taking one of these antihistamines may drink then drive within the legal limit but the effects of the alcohol may be exaggerated by the presence of the antihistamine, causing dangerous effects on psychomotor function."

COMPLAINT

The statement in question was referenced to a paper by Ramaekers *et al* (1992) and UCB pointed out that in the discussion section the authors had stated "The practical relevance of these results should not be exaggerated." UCB pointed out that the statement in the advertisement did not reflect this comment.

UCB alleged that the statement in question was contradicted by the findings of other studies. This included a recent publication which was a study conducted by a competitor company (Patat A *et al*, 1995). The studies all concluded that the administration of cetirizine at its licensed dose did not affect driving ability or interact with alcohol. This conclusion was confirmed in the publications of Hindmarch (1995), who was

extensively quoted in Schering-Plough's advertisement, Volkerts (1995) and Passalacqua *et al* (1996) who had reviewed all the available published information concerning this topic and who all produced conclusions contrary to Schering-Plough's statement.

UCB alleged that the statement was not accurate, balanced, fair or objective in breach of Clause 7.2 of the Code.

UCB was particularly concerned by the implication that the use of cetirizine could be dangerous. Such a disparaging and misleading reference was in breach of Clause 8 of the Code.

RESPONSE

Schering-Plough noted the implied allegation that it had exaggerated the clinical relevance of the Ramaekers paper. The company said that some other quotes from the paper would perhaps show that no exaggeration was involved when it had suggested that dangerous effects on psychomotor functions resulted when combining cetirizine with alcohol

"The effects of cetirizine on driving performance resembled those of alcohol .... The effects of alcohol and cetirizine appeared to be additive."

"Three driving tests were stopped by the instructor, who considered that the subjects were becoming too drowsy to continue safely. They occurred twice after the combination of placebo and alcohol and once after cetirizine ..."

"The conclusion appears inescapable: after single recommended doses cetirizine is sedative and impairing whereas loratadine is not."

Schering-Plough also noted that UCB had referred to other studies which did not reach the same conclusion. This was addressed by Ramaekers *et al* (1992) who commented:

"Ostensibly well-controlled studies ... failed to show any significant effects in various short-term psychometric tests ... The question is why acute impairment by [cetirizine] was observed here but not previously. The answer may lie in the duration and monotonous nature of the highway driving test. It lasted 6-12 times longer than most conventional psychometric tests used to assess drug effects ... Without the diverse and mutually supportive results obtained during the driving test, we would have had to join previous investigators in concluding that cetirizine 10mg had little or no effect on performance."

Schering-Plough said that another way of expressing this was the well-known conclusion that because a study failed to demonstrate an effect of a medicine did not mean the effect did not exist. It could be that, for example, the methodology of the study was flawed, or that insufficient patients were included in the study to reach a statistically significant result.

Schering-Plough also noted that the majority of the studies referred to by UCB did not relate to the effects of cetirizine and alcohol in combination, but to cetirizine alone.

Schering-Plough submitted that further evidence as to the advertisement's accuracy was provided by the labelling of cetirizine in other countries. The advertisement made reference to the USA. Here some antihistamines classified in the UK as non-sedating were classed as sedating, cetirizine being a case in point. The US labelling for Zyrtec (Zirtek) stated:

"PRECAUTIONS: Activities Requiring Mental Alertness: In clinical trials the occurrence of somnolence has been reported in some patients taking Zyrtec. Due caution should, therefore, be exercised when driving a car or operating potentially hazardous machinery. Concurrent use of Zyrtec with alcohol or other CNS depressants should be avoided because additional reductions in alertness and additional impairment of CNS performance may occur."

"ADVERSE REACTIONS ... The most common adverse reaction that occurred more frequently on cetirizine than placebo was somnolence. The incidence of somnolence associated with Zyrtec was dose related, 6% in placebo, 11% at 5mg and 14% and 10mg."

Schering-Plough said that this view of Zirtek as sedating and such effect being additive to the effects of alcohol was accepted by many UK experts, including a consultant clinical immunologist, who had written a review on this subject in a bulletin entitled "Regional Therapeutic News". A copy of the review was provided.

In the context of an advertisement which aimed to help GPs advise patients travelling abroad of potential pitfalls of taking various prescription medicines, Schering-Plough did not consider that it had breached either Clause 7 or Clause 8 of the Code. The advertisement did not imply that the use of cetirizine *per se* was dangerous, as might be inferred from UCB's complaint, but that when combined with alcohol it had the potential to be dangerous if the subject were to drive a car or other motor vehicle. This was a factual and accurate comment, as the Ramaekers paper and the US labelling for Zyrtec (Zirtek) clearly showed.

PANEL RULING

The Panel noted that the data sheet for Zirtek (Ref ABPI Compendium of Data Sheets and Summaries of Product Characteristics) stated that the product had "a low potential for drowsiness" and that "As with other antihistamines it is advisable to avoid excessive alcohol consumption".

The Panel noted that the statement in question was referenced to a paper by Ramaekers *et al*. The study had compared the effects of loratadine and cetirizine, with and without alcohol, on driving and psychometric test performance, and EEG, during driving in sixteen healthy volunteers. The paper stated that "neither antihistamine potentiated the effect of alcohol". The authors concluded that "the effects of alcohol and cetirizine appeared to be additive" and that "cetirizine, but not loratadine, generally caused mild impairment of performance after a single 10mg dose".

The Panel noted that the Patat *et al* (1995) study stated that neither of the antihistamines tested (mizolastine and cetirizine) potentiated the impairment of skilled performance and driving caused by ethanol. The CNS effect of the combination was similar to that produced by alcohol alone. Some of the studies referred to by UCB did

not relate to the effects of cetirizine and alcohol in combination but to cetirizine alone.

The Panel noted that the statement in question referred to the potentiation of alcohol's adverse effects by cetirizine. There was some evidence that the effects of cetirizine and alcohol were additive but not that cetirizine potentiated the effects of alcohol. In the Panel's view the statement in question implied that their effects were more than additive. The Panel considered that the tone of the statement implied that alcohol and driving were expressly prohibited in patients taking Zirtek which was not so in the UK. The Panel acknowledged that patients should be warned of the possibility of impairment of performance. The Panel did not consider that the statement accurately reflected the data regarding cetirizine, alcohol and driving and ruled a breach of Clause 7.2 of the Code. The Panel did not accept that the statement was disparaging as alleged and no breach of Clause 8.1 was ruled.

APPEAL BY SCHERING-PLOUGH

Schering-Plough appealed against the Panel's ruling of a breach of Clause 7.2 of the Code.

a) "The Panel considered that the tone of the statement implied that alcohol and driving were expressly prohibited in patients taking Zirtek which was not so in the UK."

Schering-Plough was baffled as to the logic leading to this conclusion. Nowhere in this statement did Schering-Plough refer to any legal or regulatory body and it had asked several other people not connected with this case if they would draw the same inference and not one had.

b) The Panel accepted that there was evidence that the effects of cetirizine and alcohol were additive, but suggested that the statement implied that their effects were more than additive.

Schering-Plough was presuming that this conclusion was based on the words "potentiating" and "exaggerated" as used in the statement in question, and that the Panel was assuming that the use of one or both of these words meant that a synergistic effect existed. However, Chambers' 21st Century Dictionary (1996 Edition) had the following definitions amongst the three applying to "exaggerate":

"Exaggerate ... to emphasise something or make it more noticeable"

Schering-Plough believed that this definition incorporated with ease the acknowledged situation that co-administration of alcohol and cetirizine had been shown to produce a greater impairment of driving skills than either of these agents when administered alone, and that there was no implication that the effects were more than additive.

Chambers' Dictionary, in common with most commonly used dictionaries, did not give a definition of "potentiate". However, the Concise Oxford Dictionary gave the following definition:

"Potentiate ... endow (esp. drug) with (more) power; make possible"

"make possible" suggested the meaning Schering-Plough was intending to convey with its description of the interaction between alcohol and cetirizine.

Schering-Plough said that it should also be mentioned for the sake of completeness that a study performed by Riedel, Veggel and O'Hanlon did find that "the combination of alcohol and cetirizine produced a bigger performance impairment than the sum of the independent effects of alcohol alone and cetirizine alone." Therefore, although Schering-Plough was not trying to imply synergy, if someone were to misinterpret its feature to mean this, some evidence existed to suggest this might be the case.

There were serious public safety considerations here which should not be lost in a semantic debate. It was true to say that there was evidence that the interaction between alcohol and cetirizine resulted in danger to an individual taking both and then driving and that this danger was greater than with either agent alone. This was what Schering-Plough meant to say and it believed most people, medically qualified or otherwise, would accept the advertisement feature as demonstrating this without the additional "implications" of words or "tone" referred to in the Panel's decision.

APPEAL BY UCB PHARMA

UCB appealed against the Panel's ruling that there had been no breach of Clause 8.1 of the Code.

UCB believed that one of the primary objectives of the material was to give the impression that combining cetirizine with alcohol could be dangerous. This belief was clearly substantiated in Schering-Plough's response which stated:

"...no exaggeration is involved when we suggest that dangerous effects on psychomotor function result when combining cetirizine with alcohol".

UCB noted that this statement did not include any modifying phrases such as "occasionally under certain circumstances, potentially, etc". It was UCB's belief that there could be no greater "knocking" of a competitor's product than to claim that its use was potentially dangerous.

This viewpoint should also be considered in the light of the Panel's conclusion that the statement breached Clause 7.2 as it did not accurately reflect the data regarding cetirizine and alcohol. UCB would submit that the Panel, in reaching its decision, should also have taken into account the supplementary information to Clause 8.1 which stated, *inter alia*, that "Provided that such critical references to another company's products are accurate, balanced, fair, etc and can be substantiated they are acceptable under the Code." Given the facts that the statement was held by the Panel to have not been accurate, was not substantiated and the tone of the statement was specifically directed to cetirizine, it was therefore inconsistent and unreasonable, in light of the Code's own guidance notes on interpretation and, more importantly, with the findings of the Panel, for the Panel to conclude that the reference did not amount to a disparaging reference or "unjustified knocking copy".

UCB requested that the Appeal Board consider the following issues which were used by Schering-Plough to defend its use of the advertisement.

a) Much of Schering-Plough's defence of the study

referred to in its feature concerned the author's comments concerning previous studies. UCB pointed out that this particular study was published in 1992 whereas all of the review articles and some of the individual studies which UCB used to support its position that the advertisement was misleading were published at a later date, ie the reviewers would have been aware of these comments.

b) In much of the "advertisement feature", and in Schering-Plough's formal reply, considerable reference was made to the United States. In order to prevent any potential misunderstanding the Appeal Board might well wish to consider the fact that the FDA had not required that cetirizine carry a 'hazard triangle' in the US. UCB was also unaware of any specific mention of cetirizine being included in any official publication produced by the FDA, or any US state, which contained a list of medications which might not be taken when driving in the US.

Further, it was UCB's understanding that the FDA had not developed any classification scheme to categorise antihistamines as sedating or non-sedating. In support of this, UCB submitted a copy of a letter from the FDA to Schering Corporation dated 24 September 1996. The letter had been referred to in open Court recently in proceedings in Holland. The letter stated:

"Contrary to Schering's assertions, FDA has not developed any such classification scheme to categorise antihistamines as sedating versus non-sedating drugs. Therefore, any suggestion, statement or representation that FDA has classified antihistamine drugs into categories of sedating or non-sedating would be false and/or misleading."

Notwithstanding the notice received from the FDA, Schering-Plough stated in its response to the Panel that:

"Further evidence as to the advertisement's accuracy is provided by the labelling of cetirizine in other countries. The advertisement makes reference to the USA. Here some antihistamines classified in the UK as non-sedating are classed as sedating, cetirizine being a case in point."

In the circumstances, UCB submitted that the Appeal Board should have regard to the advice issued by the FDA and hold that the statement at issue was not only false and misleading but clearly disparaging and in breach of Clause 8.1 of the Code.

c) In Schering-Plough's reply reference was made to a 'bulletin' containing an article by a consultant clinical immunologist. UCB noted that the 'bulletin' would appear to be a promotional item produced on behalf of Schering-Plough.

Furthermore the Appeal Board might also wish to consider the wider matter of whether any promotional material for pharmaceutical products should ever be suggesting that drinking and driving was safe, whether or not certain medications were taken. UCB believed that the advice given within the UK data sheet for cetirizine that "As with other antihistamines it is advisable to avoid excessive alcohol consumption" was ethically the right message for all manufacturers of antihistamines and indeed all drugs.

In summary, for the reasons given by the Panel in support of its rulings that the statement breached Clause 7.2 of the Code, it seemed illogical to conclude that there was no breach of Clause 8.1 of the Code. As the statement by Schering-Plough then went on to claim that this could lead to dangerous effects, UCB believed that this could clearly be described as being disparaging or unjustified knocking copy as described in the supplementary information to Clause 8.1.

RESPONSE FROM SCHERING-PLOUGH

Schering-Plough stated that much was made by UCB of the lack of modifying phrases and the allegation was made that the original advertisement feature consisted of "knocking copy". In addition there was much discussion about the classification of antihistamines as sedating or non-sedating in the US. In that context it was interesting to read the Brief Summary of Zyrtec prescribing information posted on the Internet by UCB and its partner Pfizer Inc:

"PRECAUTIONS: Activities Requiring Mental Alertness: In clinical trials, the occurrence of somnolence has been reported in some patients taking ZYRTEC; due caution should therefore be exercised when driving a car or operating potentially dangerous machinery. Concurrent use of ZYRTEC or alcohol or other CNS depressants should be avoided because additional impairments of CNS performance may occur."

and later:

"ADVERSE REACTIONS ... The most common adverse reaction that occurred more frequently on cetirizine than placebo was somnolence. The incidence of somnolence associated with ZYRTEC was dose related, 6% in placebo, 11% at 5mg and 14% at 10mg." (10mg was the dose used in the UK and most of the rest of the world.)

A copy of this prescribing information, based on the PDR entry for Zyrtec, was provided.

The bulletin written by consultant clinical immunologist was indeed sponsored by Schering-Plough. However, the consultant was a highly regarded independent allergist, and the implication that he would distort the facts because of Schering-Plough's sponsorship was offensive to Schering-Plough and would doubtless be so to him also.

Schering-Plough did not, of course, condone drinking and driving, but Claritin did not impact on driving performance at therapeutic doses, and therefore did not have an additive effect on the effect of alcohol on driving performance. Zirtek did and there was reasonable evidence that this effect was at least additive to that of alcohol. Therefore it was not unreasonable that Zirtek's labelling on this matter should differ from the non-sedating antihistamines such as loratadine or terfenadine.

Schering-Plough therefore believed that the Panel was correct in ruling no breach of Clause 8.1.

APPEAL BOARD RULING

The Appeal Board noted that the advertisement referred to antihistamines in general and while there were a number of antihistamines available cetirizine was the only competitor product named. The statement in question referred to the fact that certain antihistamines might interact with alcohol but cetirizine was the only example given.

The Appeal Board noted that it had to take account of the UK Summary of Product Characteristics (SPC) or data sheet as being the agreed details about a product. Information from countries other than the UK might be of interest but the UK SPC or data sheet information took priority.

The Appeal Board noted that the Zirtek data sheet described cetirizine as "...a potent antihistamine with a low potential for drowsiness..." and that "As with other antihistamines it is advisable to avoid excessive alcohol consumption".

The Appeal Board considered that the statement at issue gave the impression that there were major problems with the product which was not so. The Appeal Board did not consider that the statement accurately reflected the Zirtek data sheet and upheld the Panel's ruling of a breach of Clause 7.2 of the Code.

The respondent's appeal therefore failed.

The Appeal Board considered that the statement was disparaging as alleged and therefore ruled a breach of Clause 8.1 of the Code.

The complainant's appeal was therefore successful.

B HELTER-SKELTER ADVERTISEMENT

A full page advertisement, headed "For a helter-skelter belter of a summer", appeared in Doctor (19 June 1997).

3 "Depend on the world's leading antihistamine"

COMPLAINT

UCB said that this was an exaggerated and all embracing claim, as well as being a superlative. As Schering-Plough had made no effort to substantiate the merits, qualities or properties apparently attributed to Clarityn, UCB alleged a breach of Clause 7.8 of the Code of Practice.

RESPONSE

Schering-Plough said it regarded this phrase as an exhortation rather than a claim. The sentence referred to the fact that Clarityn was, by far, the most popular antihistamine globally in terms of prescription and OTC purchase, and this could be substantiated by the IMS data provided. Schering-Plough considered that the complaint was invalid.

PANEL RULING

The Panel noted that the IMS data supplied by Schering-Plough gave the moving annual totals of a number of branded antihistamines in terms of US dollars. It noted the submission that Clarityn was the most popular antihistamine globally in terms of prescription and OTC purchase. The Panel considered that the meaning of the phrase "the world's leading antihistamine" was not clear. It could be taken to mean that the product sold more doses than any other product or it could be taken to mean that it was generally regarded as being the best product. It was unlikely that readers would interpret the phrase as Schering Plough intended. In the Panel's view if the phrase was meant to refer to the fact that Clarityn was the brand leader in total cash sales in 33 countries then this should have been explicitly stated.

The Panel considered that the phrase claimed a special merit which had not been substantiated. A breach of Clause 7.8 of the Code was ruled.

Complaint received 7 July 1997

Case completed 11 November 1997

CASE AUTH/577/7/97

NO BREACH OF THE CODE

GENERAL PRACTITIONER v ELAN PHARMA

Conduct of representatives

A general practitioner complained about a representative from Elan Pharma and her field trainer alleging that, following a discussion about the use of Elan's product Dilzem SR, they had said that they would see the practice manager with a view to changing, via a computer switch, patients on Tildiem, Adizem and generic diltiazem to Dilzem SR. The complainant was not prepared to make a change via a computer switch as he would rather see the patient if he was going to change any medication.

The Panel noted that it was difficult in such cases to know what exactly had transpired between the parties, accounts differed, but considered that, as the complainant had been left with the impression that the representatives would see the practice manager about the switch when the complainant was not prepared to do it, the representatives had not maintained a high standard of ethical conduct. A breach of the Code was ruled.

Upon appeal by Elan, the Appeal Board noted that while it was unfortunate that the complainant had been left with the impression that the representative would go straight to the practice manager and effect a computer switch, this was not what was intended and not what had happened. The Appeal Board considered that there had been a genuine misunderstanding. This was unfortunate but it did not amount to a breach of the Code.

COMPLAINT

A general practitioner submitted a complaint about a representative from Elan Pharma Limited promoting Dilzem SR. The representative had been accompanied by her field trainer.

The complainant was asked directly whether he would consider changing, via a computer switch, patients from Tildiem, Adizem and generic diltiazem to Dilzem SR. The complainant made it quite clear that he was not prepared to just change people via a computer switch, as he would rather see the patient himself if he was going to change any medication. Furthermore, the reason for the change was not, as far as the complainant could see, of any benefit to the practice or the patients. It was purely to get people switched to Elan Pharma products. When the complainant said that he was not prepared to do a computer search and switch, the representatives said that they would make an appointment to see the practice manager and get her to do a computer search and switch.

The complainant alleged that the representatives' actions were totally against the Code. If a doctor made it quite clear that he was not prepared to change any patient's medication without consulting with them first, then the representative and her field trainer should not have attempted to go over the complainant's head and ask the practice manager to do the change. Furthermore, the complainant did not think that it was ethical that a practice manager should be prescribing medicines as he would hate to contemplate the legal situation should a patient have an adverse reaction to a medicine prescribed by the practice manager for which the doctor had signed the prescription.

The complainant alleged a breach of Clause 2 of the Code as he believed that promoting products by getting practice managers to change from one product to another brought discredit upon and certainly reduced his confidence in the pharmaceutical industry.

A breach of Clause 15.2 of the Code was alleged as the complainant did not believe that going over the doctor's head to the practice manager to get products prescribed constituted a high standard of ethical conduct. On the contrary, this was a very low standard of a very low ethical conduct.

The complainant drew attention to Clause 15.10 of the Code which stated that companies were responsible for the activities of their representatives if these were within the scope of their employment, even if they were acting contrary to the instructions which they had been given. Elan Pharma was, therefore, responsible for the activities of the two representatives.

However, the complainant could not believe that any ethical pharmaceutical company would be encouraging representatives and managers to firstly ask doctors to do a switch and secondly when the doctors were not happy to do this they were quite prepared to go to the practice managers to get them to do the switch.

RESPONSE

Elan Pharma asked both the representative and her field trainer for their account of the visit in order to fully understand the background. The company submitted that the response of the representatives suggested a very different, but consistent, point of view to the sequence suggested in the complaint. The e-mail feedback from both Elan representatives was provided.

The representative stated that she was very surprised by the allegation. The representative said the whole detail was friendly. The complainant said he liked and used a fair amount of Dilzem and so the representative suggested the idea of a practice conversion. The field trainer told the complainant about a conversion she had carried out and gave him a rough estimate of the amount of money he could save. He said he was now very interested but was not too confident with the technical side of the conversion as the computer and formulary matters were usually dealt with by the practice manager. The representative said that the complainant suggested that she took the matter up with the practice manager. The representative then proceeded to detail the remaining three products and another five minutes or so was spent with social chat. The representative said that at no point during the detail did the complainant seem at all irritated by the conduct. The representative did not actually go and see the practice manager as she was unavailable the following week and then the representative discovered the practice would no longer be on her territory. The representative stated that on previous visits the

complainant had complained about the conduct of other representatives in a very "gossipy" way. She had heard that another company's representative had offered to take her manager to help the complainant make a complaint against her but being gossip the representative had not taken too much notice.

The field trainer stated that the complainant was extremely friendly and the call lasted for approximately 20 minutes and at no point was any annoyance expressed at their presence. The field trainer said that the complainant chatted with them before, during and after the product detail about sport. Dilzem was detailed first and the complainant expressed an interest in the cost benefit. At this point the subject of a practice conversion was raised. The complainant asked how much he could save. As the representative had never done a practice conversion before, the field trainer told the complainant the cost-savings of a recent conversion she had done. The complainant said that he was not comfortable with the workings of the computer and the person to discuss this with would be the practice manager. At no point did the complainant say that he could not see a benefit in Dilzem as he said he already used it because he was friends with the last representative. The complainant was happy for the representative to continue to detail the other three products.

Elan stated that typically the involvement of the practice manager was the route demanded in a surgery after the doctor had been convinced of the savings and had authorised the involvement of their practice manager. Elan submitted that its representatives adhered strictly to this protocol at all times.

Both Elan representatives had passed the ABPI examination with distinction.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant stated that having read the response from Elan Pharma, the representatives' statements were not exactly what happened. The complainant strongly disagreed with the comment that the computer and formulary matters were usually dealt with by the practice manager. The complainant agreed that his technical knowledge of the computer was not a hundred per cent but what he did not agree with was doing a computer switch *per se*. The complainant was sure that he mentioned that he preferred to see the patient to explain what was happening. It was at this point that the Elan Pharma representatives said they would contact the practice manager. He did not suggest that they took the matter up with the practice manager. It was the representatives themselves who said that they would do this.

The complainant stated the point he was making was that he considered the representatives were going over his head. Once he had said no to their suggested switch, then the representatives were quite prepared to go over his head and get the practice manager to do something which the complainant strongly opposed. This was the basis of the complaint.

The complainant stated that it was only after the representatives left the room that he realised just exactly what they were proposing. He was annoyed with himself after they had left because he did not fully realise what they had said whilst in the room and he should have really picked them up on this while they were still present. The complainant made another point that, just because an interview between a GP and a representative was conducted in a friendly manner, this did not mean that the parties concerned had not adhered to the Code.

The complainant questioned the representatives statement that in previous visits he had complained about the comments of other representatives in a very "gossipy" way. The complainant would like her to expand on this and advise which representatives and which companies she was referring to and if she could also let him know the number of times she had seen him prior to the incident on 17 April 1997. The complainant stated that he did not need another company's representative or field trainer to assist him in making a complaint. Long before he saw the other company's representative he had decided to lodge the complaint and would like to make it clear that in no way did the other company's representative or her field trainer have any influence in his actions in this matter.

PANEL RULING

The Panel observed that it was difficult in such cases to know exactly what had transpired between the parties. Accounts differed. A judgement had to be made on the evidence which was available, bearing in mind that extreme dissatisfaction was usually necessary on the part of an individual before he or she was moved to actually submit a complaint.

The Panel noted that the complainant said that he had made it quite clear that he was not prepared to just change patients' medication via a computer switch whereas the representative had said that he was interested in a conversion but was not too confident with the technical side. The complainant did not agree with the representative's view that the complainant had said that computer and formulary matters were usually dealt with by the practice manager.

The Panel considered that the interview had not been satisfactory. There had been a misunderstanding as to the policy regarding therapy switches and whether the complainant had recommended that an appointment be made with the practice manager or whether the representatives themselves had made that suggestion.

The Panel noted the submission from Elan Pharma that the involvement of the practice manager was the route usually required in a surgery after the doctor had been convinced of the savings and had authorised the involvement of the practice manager.

The Panel considered that as the complainant had been left with the impression that the representatives would contact the practice manager about the computer switch when he was not prepared to do a computer switch, the representatives had not maintained a high standard of ethical conduct. The Panel therefore ruled a breach of Clause 15.2 of the Code. The Panel did not accept that the circumstances were in breach of Clause 2 of the Code and no breach of that clause was ruled.

APPEAL BY ELAN PHARMA

Elan Pharma said that following feedback from the

representatives involved, copies of which were provided, and discussions with them, it had been concluded that the ruling was unfair. A number of points had been made.

- The period of time taken by the complainant to register his complaint (7 weeks) did not suggest any initial concern.
- Between the time of the visit (17 April) and the arrival of the complaint on 8 July [the letter was dated 4 June 1997] Elan Pharma's representative did not pursue the practice manager - hardly suggesting any 'pushiness' or desire to proceed in an inappropriate manner.
- The General Manager of Elan Pharma had been impressed by the clear and consistent recall of the meeting by its two representatives.
- The experience, ethics and integrity of the Elan Pharma people - if the approach they had been accused of taking had been their *modus operandi*, it was reasonable to expect other clinicians would have complained about their behaviour.

The representative and the field trainer both provided further detailed comments on the interview.

The company provided the Appeal Board with notes of a meeting between the Regional Manager of Elan Pharma and the representatives in question, together with the representatives' computer files and internal company correspondence.

APPEAL BOARD RULING

The Appeal Board noted that it was becoming increasingly common for representatives to liaise with GPs to effect a computer switch so that all prescriptions in a particular practice for a particular medicine were written for one product. In the Appeal Board's view such an activity was not in breach of the Code *per se* but representatives must be careful about the methods they employed.

The Appeal Board noted that the representative and her trainer had called on the complainant on 17 April 1997 but his letter of complaint had not been written until 4 June 1997. It had arrived at the Authority on 8 July 1997. It further noted that the complainant had not appealed the Panel's ruling of no breach of Clause 2 of the Code. The Appeal Board considered that had the representative wanted to contact the practice manager to effect a computer switch then she had had ample time to do that between her visit to the complainant and his complaint being submitted to the Authority. The Appeal Board noted that the representative had not contacted the practice manager.

The Appeal Board noted that while it was unfortunate that the complainant had been left with the impression that the representative would go straight to the practice manager to effect a computer switch this was not what was intended nor what had happened.

The Appeal Board considered that there had been a genuine misunderstanding. This was unfortunate but it did not amount to a breach of the Code. The Appeal Board therefore ruled no breach of Clause 15.2.

The appeal was therefore successful.

Complaint received **8 July 1997**

Case completed **13 November 1997**

SEARLE v BOEHRINGER INGELHEIM

Mobic advertisement

Searle alleged that an advertisement for Mobic issued by Boehringer Ingelheim was misleading and implied a special merit for Mobic which was unsubstantiated in clinical practice.

The Panel ruled that the advertisement was misleading in breach of the Code due to the lack of clinical data to confirm a hypothesis that NSAIDs which selectively inhibited COX-2 could have a better side-effect profile. The Panel also ruled a breach as the advertisement in effect described Mobic as a "Red carpet treatment" which was exaggerated and implied a special merit for the product that could not be substantiated.

On appeal by Boehringer Ingelheim, the Appeal Board considered that as there was clinical evidence to show an improved gastrointestinal side-effect profile for Mobic, the advertisement was not misleading in referring to theoretical advantages of selective COX-2 inhibition bearing in mind that it was made sufficiently clear there were no data to link the two. The Appeal Board noted that the red carpet image in the advertisement related to the one third reduction in gastrointestinal side-effects compared to other commonly used NSAIDs. Given the data it was not unreasonable to refer to Mobic as a "Red carpet treatment". The Appeal Board ruled no breach of the Code.

Searle complained about a journal advertisement for Mobic (ref BIL MOB0010) which had been issued by Boehringer Ingelheim Limited and which appeared in Pulse, 5 July 1997. Across the two pages the advertisement was headed "COX inhibition - what is your preference?" underneath which was a visual of a red carpet rolling out. The left hand page of the advertisement referred to cyclo-oxygenase (COX) and discussed the discovery and theory of COX-1 and COX-2 inhibition. The last paragraph of the text read "Theoretically NSAIDs which selectively inhibit COX-2 could have a better GI side effect profile. However, there are no clinical data to confirm that this hypothesis is correct". On the right hand page was "Mobic" in logo type underneath which was the claim "Red carpet treatment".

COMPLAINT

Searle stated that this form of advertising by Boehringer Ingelheim appeared to be part of a multinational concerted campaign to promote Mobic on the back of *in vitro* data and a hypothesis which suggested improved safety (less NSAID-induced ulceration and GI complications such as perforation/bleeding), but which had not yet been supported by clinical data for the product.

Searle noted that the Appeal Board had ruled against Boehringer Ingelheim on a similar matter relating to pre-launch material for Mobic in November 1996 (Case AUTH/455/8/96).

Searle said that from the time of launch in the UK, Boehringer Ingelheim had continued to promote and detail on the basis of the linkage of selective COX-2 inhibition and improved GI safety for its product (over existing NSAIDs). This had been the subject of extensive discussion between the two companies and Searle had endeavoured on numerous occasions to resolve these issues with Boehringer Ingelheim. Boehringer Ingelheim had given various assurances about its promotion, and that the *in vitro* pharmacological effects regarding selective inhibition of COX-2 would not be linked to unsubstantiated claims for improved clinical safety. In particular Boehringer Ingelheim had agreed that COX-inhibition data would only be used in context and that representatives would not use a monograph which specifically linked COX-2 inhibition and claims for clinical safety.

Searle said that in November 1996 the two companies had also discussed what message the representatives from Boehringer Ingelheim were conveying to doctors. Market research information from 'Detail Monitor' indicated that some 50% of details recalled by doctors cited linkage between COX-2 selective inhibition and improved GI safety. Both parties agreed that the results from 'Detail Monitor' should continue to be reviewed.

Searle said that such detailing appeared to have continued unabated, and in May 1997 it wrote to Boehringer Ingelheim with specific points about the detailing. A copy of the letter was provided.

Searle said that in summary, in the first quarter of 1997, 1168 GPs submitted answers for the standard 'Detail Monitor' questionnaire. This asked GPs whether representatives from any company discussed their products/services in the past week. The third question asked for the main points recalled about the product in question, and the fourth asked about the doctor's reactions. Of the 1168 doctors, 47 mentioned Mobic and Searle considered that at least 30 of these indicated detailing which involved linkage of COX-2 inhibition with improved clinical safety. Boehringer Ingelheim disagreed with these findings.

Searle said that there had been parallel promotions in other European countries, and rulings given out in Sweden and Holland against the similar COX-2/GI safety linkage. In the Dutch case this had resulted in a letter being sent out by Boehringer Ingelheim to rheumatologists to clarify the situation regarding Mobic.

Searle said that against this background of discussion, and despite prior rulings, promotion had continued along the same theme, and it was in this context that Searle had reviewed this new Mobic advertisement. Searle could see no alternative but to bring the matter to the Authority.

The specific comments Searle had about the advertisement were as follows:

The title line, "COX inhibition - what is your preference?", made no claim, but was a subtle play on words and implied that Mobic provided some form of preferential treatment. This was reinforced by the use of the red carpet

motif and the statement "Mobic Red carpet treatment". The 'red carpet' had been a theme throughout the promotion of Mobic, and Searle enclosed copies of two photographs of part of a stand used in Northern Ireland by Boehringer Ingelheim (the inappropriate use of which was acknowledged by Boehringer Ingelheim). One photograph showed the red carpet and the terminology "This way for preferential treatment" and the carpet rolled up in the background. The other photograph showed the preferential COX-2 wording used and the 'preferential treatment' indicated on their main slogan. The current advertisement was clearly continuing this same theme.

Searle noted that the bottom left part of the advertisement contained text which focused solely on COX-1 and COX-2 and the theory that selective COX-2 inhibition could result in a better GI side effect profile. The text went on to say that there were no clinical data to confirm that this hypothesis was correct. This latter statement appeared to be one that had been included as a result of external pressures.

Searle said that the advertisement clearly raised the question as to why some special merit in the form of red carpet treatment was being implied, even in the absence of clinical evidence. If it was argued that there was no linkage between the text and the headline and the statement that Mobic represented red carpet treatment, then why were these items all mentioned on the same advertisement?

Searle said that it had discussed various objections about the same theme of promotion - the relating of in-vitro COX-2 inhibition data to an unsubstantiated clinical claim - over several months with Boehringer Ingelheim.

It appeared to Searle that a clear linkage was being made with a promotion that was designed to mislead and imply GI safety which was in fact unsubstantiated by clinical evidence. The evidence from 'Detail Monitor' reinforced this impression.

Searle said that in view of the orchestrated nature of this form of campaign in the UK and elsewhere, it considered that the promotion overstepped the bounds of what was acceptable within the industry and was in danger of jeopardising the credibility of the scientific base upon which pharmaceuticals must be founded and must be seen to be founded by the medical fraternity.

Searle alleged that the advertisement was both misleading, in breach of Clause 7.2 of the Code, and implied a special merit for Mobic which was unsubstantiated in clinical practice in breach of Clause 7.8.

RESPONSE

Boehringer Ingelheim noted that Searle had alleged that the advertisement for Mobic was misleading and implied a special merit for the product unsubstantiated in clinical practice. Boehringer Ingelheim also noted that Searle had implied that by previous rulings of the Panel on earlier Mobic promotion, by the activities of Boehringer Ingelheim affiliated companies outside the UK and by crude analysis of records from a market research organisation, that the promotion of Mobic was in some way inappropriate, thus confirming the allegations with respect to the advertisement.

Boehringer Ingelheim drew attention to the fact that following previous rulings by the Panel and the Appeal Board all advertising for Mobic was withdrawn. During subsequent dialogue with the Medicines Control Agency (MCA) agreement was reached on the content of new promotional material for Mobic and the company was routinely in discussion with the MCA for future promotional material. The advertisement in question was one that the MCA had not found objectionable.

With regard to the alleged breaches of the Code Boehringer Ingelheim noted that the advertisement included a headline "COX inhibition - what is your preference?", an unrolling red carpet theme and the logo Mobic meloxicam above the words "Red carpet treatment". Information was also provided as to the state of scientific investigation of cyclo-oxygenase (COX) inhibition with the very clear statement that the hypothesis generated by the discovery of two isoforms of the enzyme had not been confirmed by clinical data.

Boehringer Ingelheim said that the facts were as follows:

1 All NSAID treatments were known to be cyclo-oxygenase inhibitors and the rhetorical question posed to the reader was therefore quite straightforward - COX inhibition - which one do you, the prescriber, prefer?

2 The red carpet theme and the wording "Red carpet treatment" implied some merit which should influence the prescriber's preference. The data which supported this implied claim related to gastrointestinal tolerance and were twofold. Firstly in a pooled analysis by Distel *et al* (1996), already made available to Searle, Mobic was shown at both approved doses to be associated with less gastrointestinal side-effects in randomised controlled trials. Secondly two large-scale comparative trials had been conducted in symptomatic osteoarthritis designed to assess the tolerance of Mobic 7.5 mg compared to, on the one hand, diclofenac 100mg SR and, on the other, piroxicam 20mg. Preliminary results of these two trials known as MELISSA and SELECT were available upon request and manuscripts had been submitted/were in preparation for publication. The data showed that over a four week exposure significantly fewer patients receiving Mobic complained of gastrointestinal side effects than those receiving either diclofenac or piroxicam. It should be noted that the former was the market leading drug in the UK and the latter was widely prescribed in continental Europe. Gastrointestinal tolerance was considered by many doctors to be a greater barrier to successful treatment than the more serious outcomes of ulceration with bleeding or perforation.

Boehringer Ingelheim rejected the allegations made by Searle and asserted that its advertisement was not in breach of the Code.

PANEL RULING

The Panel noted that the Mobic advertisement featured only on COX inhibition. The heading "COX inhibition - what is your preference?" appeared in very large bold type and the text discussing the discovery and theory of COX-1 and COX-2 inhibition was prominent enough to ensure that doctors would be drawn to read it. The Panel noted that the final paragraph of text stated that

"Theoretically NSAIDs which selectively inhibit COX-2 could have a better side effect profile. However, there are no clinical data to confirm that this hypothesis is correct.".

The Panel noted that, according to the prescribing information provided on the advertisement, Mobic was associated with GI side effects. The paper by Distel *et al*, however, showed that Mobic had an improved GI safety profile in comparison with standard doses of well established NSAIDs (piroxicam 20mg, diclofenac 100mg slow release and naproxen 750 - 1000mg) although this paper still showed an incidence of GI side effects of approximately 17% with Mobic. Boehringer Ingelheim had also supplied some unpublished confidential data to further support the fact that, although GI events did occur in patients receiving Mobic, they were less frequent than with diclofenac or piroxicam. This data was not to be passed to Searle.

The Panel considered that the impression given by the advertisement was that Mobic, possibly because of a selective inhibition of COX-2, could have an improved GI side effect profile. It was indeed difficult to see what other message the advertisement was intended to convey. The Panel noted that the advertisement did not specifically state that selective COX-2 inhibition was associated with improved GI tolerance and nor did it give the impression that Mobic was not associated with any GI effects. The Panel acknowledged that there was data from the Distel paper to support an improved GI tolerability with Mobic compared to piroxicam, diclofenac slow release and naproxen. The Panel considered, however, that the advertisement was misleading due to the lack of clinical data to confirm the hypothesis that NSAIDs which selectively inhibited COX-2 could have a better side effect profile. A breach of Clause 7.2 was ruled. In addition the Panel considered that the advertisement in effect described Mobic as a "Red carpet treatment" which was exaggerated and implied a special merit for the product that could not be substantiated. A breach of Clause 7.8 was ruled.

APPEAL BY BOEHRINGER INGELHEIM

Boehringer Ingelheim stated that Searle had sought by reference to the ruling on a previous case (AUTH/455/8/96) to contend that prescribers could be misled by the advertisement into believing that COX-2 inhibition as exhibited by Mobic conferred a particular clinical outcome on its use.

The facts were that following the outcome of the previous case Boehringer Ingelheim withdrew all promotion of Mobic and agreed with the Medicines Control Agency (MCA) to submit all material for its review and approval (or lack of objection) so as to ensure conformity with the regulations and to avoid, in the eyes of the MCA, any possibility of confusing or misleading the prescriber. The advertisement complained of by Searle was agreed with the MCA, among others, as not being misleading to prescribers or other healthcare professionals. It was therefore somewhat bewildering to receive a judgement from the Panel that the advertisement was misleading and contained an exaggerated claim.

In responding to this complaint Boehringer Ingelheim made it abundantly clear that the previous advertising had been withdrawn and the relevant undertaking been given and that no subsequent advertising had been published without the expressed opinion and acceptance by the MCA. It was therefore irrelevant to consider either the past or what might have been happening in countries for which Boehringer Ingelheim was not responsible. Nevertheless in making its judgement the Panel appeared to have been influenced precisely by that which it was requested to ignore.

Likewise this appeal against the ruling of the Panel would concern itself solely with the advertisement for Mobic prepared in June 1997 and complained of by Searle and Boehringer Ingelheim requested that the Appeal Board similarly concern itself with the question of whether that advertisement on its own was misleading, ie in breach of Clause 7.2, or made an exaggerated claim, ie in breach of Clause 7.8.

1 "The Panel considered, however, that the advertisement was misleading due to the lack of clinical data to confirm the hypothesis that NSAIDs which selectively inhibited COX-2 could have a better side-effect profile".

The ruling was in error since the advertisement actually denied the existence of clinical data which confirmed the COX-2 hypothesis. The issue was precisely that which the MCA believed had potential to mislead prescribers and the wording used was precisely that which the MCA considered was relevant and avoided the potential to mislead. There was ample evidence that Mobic preferentially inhibited COX-2 and that Mobic had an improved side-effect profile over the NSAIDs with which it had been compared.

2 "... the Panel considered that the advertisement in effect described Mobic as a "Red carpet treatment" which was exaggerated and implied a special merit for the product that could not be substantiated."

This ruling was also in error as there was no doubt that the special merit of Mobic could be substantiated if its clinical usage showed it to be superior to other agents. In fact such evidence had been produced.

All randomised clinical trials conducted with Mobic at 7.5mg meloxicam showed efficacy comparable to other NSAIDs at recommended doses, eg diclofenac, piroxicam and naproxen. Most recently in patients with symptomatic osteoarthritis involving two trials of almost 19,000 patients, meloxicam at 7.5mg daily had been shown to have efficacy equivalent to diclofenac SR 100mg once daily and piroxicam 20mg daily. Criteria for equivalence were pre-specified.

Boehringer Ingelheim submitted that any advantage in clinical profile must therefore lie with tolerability or with safety. As far as the latter was concerned pooled safety analysis suggested that meloxicam treatment might be associated with improved safety expressed as gastrointestinal bleeding or perforation. MELISSA and SELECT were short-term studies and while there were fewer serious gastrointestinal events in the meloxicam treatment arms, the differences were not statistically significant.

Gastrointestinal side-effect complaints were statistically significantly less with meloxicam when compared with diclofenac 100mg and piroxicam 20mg. Thus against diclofenac SR, considered to be one of the 'safer' NSAIDs in terms of gastrointestinal toxicity, meloxicam showed a

one third reduction (13% vs 19%) in gastro-intolerance symptomatic complaints and against piroxicam the same reduction, 10% vs 15%. Considering the numbers in the two trials these represented real improvement in the clinical risk-benefit ratio for meloxicam, given the fact that the commonest complaints that prescribers saw with NSAIDs were gastrointestinal in nature. This clinical advantage was absolutely consistent with Boehringer Ingelheim's implied clinical claim for meloxicam.

Boehringer Ingelheim confirmed that data from the MELISSA and SELECT trials was available on request to anyone who asked for it.

A one third reduction in gastrointestinal side-effects compared to other commonly used NSAIDs while preserving equal efficacy represented no small change to the risk-benefit ratio of an NSAID product. That was not an exaggerated claim and thus the red carpet image was not an unreasonable image.

In order to assist the Appeal Board, Boehringer Ingelheim had requested an independent review of the scientific and medical information from an acknowledged expert in this field.

APPEAL BOARD RULING

The Appeal Board noted that there was clinical evidence that meloxicam was better tolerated in terms of gastrointestinal side-effects than standard doses of diclofenac and piroxicam. A summary of the data from the two trials, MELISSA and SELECT, was available to all enquirers on request. The Appeal Board noted that the advertisement implied that this favourable gastrointestinal side-effect profile could theoretically be due to the fact that meloxicam selectively inhibited COX-2. The advertisement went on to state that there was no clinical data to confirm this hypothetical link.

The Appeal Board considered that as there was clinical evidence to show an improved gastrointestinal side-effect profile for Mobic the advertisement in question was not misleading in referring to the theoretical advantages of selective COX-2 inhibition bearing in mind that it was made sufficiently clear that there were no clinical data to link the two. The Appeal Board therefore ruled no breach of Clause 7.2 of the Code.

The Appeal Board noted the submission that the red carpet image in the advertisement in question related to the one third reduction in gastrointestinal side-effects compared to other commonly used NSAIDs. The Appeal Board considered that given the data it was not unreasonable to refer to Mobic as a "Red carpet treatment". The Appeal Board did not consider the phrase to be an exaggerated claim and ruled no breach of Clause 7.8.

The appeal was therefore successful.

Complaint received **15 August 1997**

Case completed **15 October 1997**

CASES AUTH/586/7/97 AND 591/7/97

GENERAL PRACTITIONER v MERCK SHARP & DOHME

Fosamax "Dear Doctor" letter and journal advertisement

A general practitioner complained about a "Dear Doctor" letter and a journal advertisement for Fosamax issued by Merck Sharp & Dohme. The complainant alleged that the materials were misleading as the results of what was described as the Landmark Fracture Intervention Trial were reported without mentioning that all the women in the trial had existing vertebral fractures.

The Panel considered that it was misleading to give the results of the trial without pointing out that the results obtained were specific to postmenopausal women with x-ray evidence of vertebral fracture. The audience should have been made aware of the specific nature of the trial population so that the results could be viewed in context. A breach of the Code was ruled. The Panel's ruling was upheld by the Appeal Board following an appeal from Merck Sharp & Dohme.

A general practitioner complained about a mailing on Fosamax sent to doctors by Merck Sharp & Dohme Limited. Following receipt of the response to the first complaint, the complainant contacted the Authority again drawing attention to a related journal advertisement.

Case AUTH/586/7/97

The promotional material at issue consisted of a "Dear Doctor" letter (ref 06-98 FSM. 97.GB.60157.M.42m.QO.697) which was sent with a leaflet (ref 11-97 FSM.96. GB.60676R.M.42m.QO.697). The materials gave details of some of the results from the Fracture Intervention Trial which had been published by Black *et al* in The Lancet, December 1996. The trial was described in the promotional material as a 'landmark' trial.

COMPLAINT

The complainant referred only to the "Dear Doctor" letter. The complainant said he was very impressed by the results of the Landmark Fracture Intervention Trial that were reported in the letter and asked the company for a reprint of the trial which was provided.

The complainant said that it was clear from reading the reprint that the "Dear Doctor" letter was seriously misleading. A breach of Clause 7.2 of the Code was alleged. The trial referred to in the "Dear Doctor" letter was called "Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures". It referred exclusively to women who had existing vertebral fractures and significant osteoporosis. The trialists commented "Our trial has several limitations. We included only postmenopausal women with low bone density and vertebral fractures.". A second arm of the trial

was designed specifically to look at women without pre-existing vertebral fractures, but that trial had not yet reported.

The complainant pointed out that nowhere in the "Dear Doctor" letter was it mentioned that all women in the trial had osteoporotic vertebral fractures at the outset. The complainant believed that this was a highly significant omission. Anybody reading the "Dear Doctor" letter would assume that any postmenopausal woman with osteoporosis would be likely to gain significant benefit from the treatment. This was clearly not what the trial showed.

RESPONSE

Merck Sharp & Dohme submitted that information quoted in the "Dear Doctor" letter by the complainant was correct and fully supported by the references quoted at the end of the prescribing information. The women included in the study were all postmenopausal by at least two years. There were a number of other inclusion and exclusion criteria for the trial described in full in the publication by Black *et al* in the methods section. The Fracture Intervention Trial had two arms, one of women without pre-existing vertebral fracture and the other of women with vertebral fractures. Apart from vertebral fracture the inclusion and exclusion criteria for the two arms were the same. Inclusion criteria were aged between 55 to 81 years at baseline, femoral neck bone mineral density (BMD) of 0.68g/cm^2 or less (corresponding to approximately two standard deviations below young adult normal as measured on a Hologic QDR - 2000 bone densitometer). The exclusion criteria were peptic ulcer disease, dyspepsia requiring daily treatment, abnormal renal function etc. Low BMD, an accepted measure of fracture risk, was the principal criteria for entry into both arms of the Fracture Intervention Trial. Thus while the vertebral fracture arm did include only women with vertebral fractures it was unrealistic to say the results bore no relation to likely effects on postmenopausal osteoporotic women without vertebral fractures. It was not reasonable, necessary or appropriate to quote all the inclusion and exclusion criteria in the "Dear Doctor" letter. For those who wished to examine the full details of the inclusion/exclusion criteria, the reference was clearly given in the text of the letter and in the reference section. Reprints of the publication were available from the company and The Lancet would be present in any medical library.

Merck Sharp & Dohme submitted that in any event the leaflet sent with the "Dear Doctor" letter mentioned on the page entitled "Proof" that women in this arm of the Fracture Intervention Trial had x-ray evidence of vertebral fracture together with some of the other inclusion criteria. Thus the information that formed the subject of the complaint was provided in the mailing.

The assumption that any postmenopausal woman with osteoporosis would be likely to gain significant benefit from the treatment was correct, except of course those where it was contraindicated, and in line with the licensed indication for Fosamax. The product was licensed for the treatment of osteoporosis in postmenopausal women. This conclusion was soundly based on all the evidence available from the Fracture Intervention Trial and other clinical trials of Fosamax. Indeed in phase III trials where only 20% of the postmenopausal women included had pre-existing vertebral fractures, the reductions in relative risk were comparable to those seen in the Fracture Intervention Trial for vertebral and multiple vertebral fractures (Liberman *et al* 48% and 86% respectively not powered to show risk of hip fracture reductions).

Case AUTH/591/7/97

COMPLAINT

The complainant wrote to extend his complaint to the advertisements appearing in the medical press. A copy of an advertisement appearing in GP, 1 August 1997, was provided (ref 11-97 FSM.96.GB.60556.J.A).

RESPONSE

Merck Sharp & Dohme Limited submitted that the advertisement was not in any way misleading. The complainant did not specify a clause alleged to have been breached and the company assumed that precisely the same complaint applied as in Case AUTH/586/7/97. The company submitted that its arguments in defence of the advertisement were clearly stated in its response to Case AUTH/586/7/97 and had nothing further to add.

PANEL RULINGS

Case AUTH/586/7/97

The Panel noted that the "Dear Doctor" letter had a large heading "The Landmark Fracture Intervention Trial" underneath which details about the trial were given. The trial was described and details of the number of patients, investigators, clinical centres, years' work and its conclusion were provided. The results in fracture reduction were also given. The Panel noted that the trial population was described as "2,027 postmenopausal women". The "Dear Doctor" letter as a whole only referred to postmenopausal women, nowhere did it state that the Fracture Intervention Trial was carried out on women with x-ray evidence of vertebral fracture. This information was however given in the leaflet which accompanied the "Dear Doctor" letter.

The Panel noted that it was a clearly established principle that each piece of promotional material had to stand alone. It was not possible to rely on information given in one item to qualify information given in another.

The Panel considered that it was misleading to give details about the trial without pointing out that the results obtained were specific to those postmenopausal women with x-ray evidence of vertebral fracture. A second arm of the trial was ongoing to include those women with no x-ray evidence of vertebral fractures. The Panel considered that while the results of the second arm might mirror those of the completed arm the very specific results reported in the letter in terms of percentage reduction in fractures at various sites would not apply. The Panel considered that readers of the letter should have been made aware of the specific nature of the trial population so that the results could be viewed in context. Fosamax was licensed to treat osteoporosis in postmenopausal

women as a whole and in the Panel's view the letter gave the impression that the results of the Fracture Intervention trial applied to this population which was not so.

The Panel considered that the "Dear Doctor" letter was misleading and therefore ruled a breach of Clause 7.2 of the Code.

Case AUTH/591/7/97

The Panel noted that the journal advertisement did not state that the women in the trial for whom the results were given in the advertisement were those who had x-ray evidence of vertebral fractures. The trial population was, again, only described as postmenopausal. The Panel considered that its ruling in Case AUTH/586/7/97 would also apply here and a breach of Clause 7.2 was therefore ruled.

APPEAL BY MERCK SHARP & DOHME

Merck Sharp & Dohme firmly believed that the materials concerned were in no way misleading and reflected the enormous wealth of clinical trial evidence for the efficacy of Fosamax .

The allegations suggested that the "Dear Doctor" letter and advertisement did not reflect the evidence available and were seriously misleading. Merck Sharp & Dohme was appealing against the ruling on the following basis:

1 The licensed indication for Fosamax was for the treatment of osteoporosis in postmenopausal women. The data provided for the licence submission, and that which had subsequently become available, supported the fact that "any post-menopausal woman with osteoporosis would be likely to gain significant benefit from the treatment".

2 Although the vertebral fracture arm of the Fracture Intervention Trial included only postmenopausal woman with a pre-existing vertebral fracture the relative risk reductions for fractures quoted were comparable to studies that had not required fracture as an entry criteria. Any differences in the exact fracture reductions were not sufficient to "seriously mislead" as to the efficacy of Fosamax as alleged.

3 This ruling would set an unreasonable precedent that would establish the requirement that all advertisements containing results of clinical trials should include all the entry criteria for the study, which Merck Sharp & Dohme believed would be unwieldy and unnecessary.

Merck Sharp & Dohme believed that "any post-menopausal woman with osteoporosis would be likely to gain significant benefit from the treatment" consistent with its licensed indication. Virtually all women (over 96%) in its phase III clinical trials had demonstrated measurable increases in their lumbar spine bone mineral density (BMD). Increases in BMD of one standard deviation (approx 10%) led to a consequent decrease in fracture risk by 50%. Only 20% of the women in these pivotal phase III studies had a pre-existing vertebral fracture. The results from the clinical fracture arm of the Fracture Intervention Trial involving over 4,400 women had just been presented at the American Society of Bone and Mineral Research (ASBMR) meeting on 14 September 1997 and had confirmed the efficacy of Fosamax in postmenopausal women without fracture. In this study there was a significant 44% reduction in the relative risk of vertebral fracture. In a subgroup analysis of women with a BMD more than 2.5 standard deviations below the young adult mean (the WHO definition of osteoporosis) hip fractures were reduced by a significant 56%. Unfortunately, the published abstract for this included only interim results, but the UCSF (University of California San Francisco) press release was provided. Merck Sharp & Dohme apologised that these results were not provided to the Panel in the initial response but they had only just been published. To summarise, the data available strongly supported the assertion that patients with or without fracture would be expected to gain significant benefit from treatment with Fosamax.

The allegation that the results quoted were "seriously misleading" could only be substantiated if the benefits observed in the vertebral arm of the Fracture Intervention Trial were markedly different from other studies. This was definitely not so. The absolute rates of fracture varied between the various studies with Fosamax, as would be expected, because of the different populations studied in each case. These absolute rates did not appear in the promotional items. However, the relative risk reductions quoted from the vertebral fracture arm of the Fracture Intervention Trial were consistent with other studies. Results were presented in a table for all Phase IIb/III Fosamax trials in postmenopausal osteoporosis. Not all of the analyses had been conducted for each study, but where data was available it was presented. The relative risk reductions presented in the mailing and the advertisement supported those seen in other Fosamax studies. Even where there seemed to be marked differences in relative risk reduction between the studies the results were not statistically significant, and were indeed greater than in the Fracture Intervention Trial (for example in the Phase III studies there was a non-significant 75% reduction in hip fractures). These results were presented for completeness. Wrist fracture results from the clinical arm of the Fracture Intervention Trial were not presented at ASBMR and so did not appear. To summarise, the relative risk reductions for Fosamax in postmenopausal osteoporosis were the same regardless of the fracture status of the patients in the studies. The absence of a statement that the vertebral fracture arm of the Fracture Intervention Trial included only women with vertebral fracture did not therefore mislead as to the efficacy of the product.

Merck Sharp & Dohme accepted the principle that each piece of promotional material should stand alone as stated in the Panel's ruling. Pointing out that a leaflet had been enclosed which included the information that the vertebral arm of the Fracture Intervention Trial included only women with fractures was not intended as a defence of the letter, rather as a point of information so that those considering the case could be in full possession of the facts. As discussed above, Merck Sharp & Dohme adamantly believed that the letter was not misleading, and its views of the letter did not rely on qualification by the leaflet.

Merck Sharp & Dohme believed the Panel's ruling would set an unreasonable precedent that would require all advertisements to include an extensive list of entry criteria, many of which were commonly employed in

pharmaceutical company clinical trials. Clinicians were familiar with this selection process for the sample population in clinical trials, and applying the results of these trials to the patients encountered in their everyday practice. Indeed, this was the essence of evidence based medicine.

To conclude the studies to establish the efficacy of Fosamax had involved almost 10,000 patients in one of the most rigorous clinical trial programmes ever conducted. The relative risk reductions for the different fractures were consistent between the various studies. Merck Sharp & Dohme believed the material complied fully with the Code.

Merck Sharp & Dohme acknowledged that the results of the clinical arm of the Fracture Intervention Trial might be different to the specific results of the vertebral arm of the Fracture Intervention Trial. The results would however be consistent.

APPEAL BOARD RULING

Case AUTH/586/7/97

The Appeal Board noted that the Fracture Intervention Trial had consisted of two arms - the vertebral fracture arm where all of the women taking part had x-ray evidence of vertebral fracture on entry, and the clinical fracture arm where the women did not have any evidence of pre-existing vertebral fractures.

The vertebral fracture arm had, on the advice of the independent Data Safety Monitoring Board, been stopped early because of the positive results. The clinical fracture arm had not been similarly stopped. It appeared to the Appeal Board that the two arms of the study had been carried out independently of one another. For the vertebral fracture arm to be completed early but not the clinical fracture arm suggested that the two study populations were seen as being different from one another.

The Appeal Board noted the submission from Merck Sharp & Dohme that the relative risk reductions for Fosamax in postmenopausal osteoporosis were the same regardless of the fracture status of the patients in studies. Approximately 20% of patients in the Phase III studies had pre-existing vertebral fractures. Results from patients with pre-existing vertebral fractures were being extrapolated to apply to the postmenopausal population as a whole. The Appeal Board queried whether data already obtained from Phase III studies could be used as a basis for predicting the results of the Fracture Intervention Trial clinical arm.

The Appeal Board considered that the omission of the pertinent details of the patients' fracture status when discussing the results of the vertebral arm of the Fracture Intervention Trial in the "Dear Doctor" letter was misleading given that data from the clinical arm was not available when the materials were issued. The company would have no way of knowing that the results from both arms of the trial would mirror each other. In the circumstances the Appeal Board considered that readers of the material should have been made aware of the specific nature of the trial population so that the results could be viewed in context.

In the Appeal Board's view the letter gave the impression that the results of the Fracture Intervention Trial applied to the treatment of osteoporosis in all postmenopausal women. This was not necessarily so.

The Appeal Board considered that the "Dear Doctor" letter was misleading and therefore upheld the Panel's ruling of a breach of Clause 7.2 of the Code.

The appeal accordingly failed.

Case AUTH/591/7/97

The Appeal Board noted that the journal advertisement did not state that the women in the trial of whom the results were given in the advertisement were those who had x-ray evidence of vertebral fractures. The trial population was, again, described as post-menopausal. The Appeal Board considered that its ruling in Case AUTH/586/7/97 would also apply here. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 of the Code.

The appeal accordingly failed.

Complaints received

Case AUTH/586/7/97	**17 July 1997**
Case AUTH/591/7/97	**31 July 1997**
Cases completed	**6 November 1997**

CASE AUTH/587/7/97

JANSSEN-CILAG v LILLY

Zyprexa booklet

Janssen-Cilag complained about a leavepiece for Zyprexa issued by Eli Lilly. The leavepiece made a number of comparisons between Zyprexa (olanzapine) and Janssen-Cilag's products haloperidol and risperidone.

Janssen-Cilag alleged that a graph which plotted the weekly improvement in positive symptoms over a six week period for Zyprexa and haloperidol was visually misleading. An asterisk was used to denote a p value which was not statistically significant. On cursory inspection the divergent lines in the graph and the inclusion of an asterisk gave the impression of a statistically significant difference between Zyprexa and haloperidol, which was not the case. The Panel noted that the p value was given in a footnote but that no mention had been made that the result was not statistically significant. The claim "At least as effective at improving positive symptoms as haloperidol" appeared beneath the graph. The Panel considered that, despite the footnote and the claim, the graph was visually misleading. A non significant result had been presented in a misleading way and a breach of the Code was ruled.

In relation to various claims of efficacy and safety for Zyprexa as compared with risperidone, it was alleged that the study to which they were referred had used a starting dose of olanzapine of 15mg whereas the starting dose in the Zyprexa SPC was 10mg. Janssen-Cilag claimed that readers were led to believe that the efficacy/ safety data reported versus risperidone was based on the usual starting dose of 10mg for Zyprexa which was not the case. The Panel noted that the final page of the leavepiece summarised the dose and use of Zyprexa and in addition to a large visual of "10mg" there was the claim "One 10mg tablet is a therapeutic dose from day one". The Panel considered that it was misleading not to have placed the preceding pages in the context of a 10mg dose. Most readers would assume that Zyprexa had been used in the study at its licensed starting dose which was not so. A breach of the Code was ruled.

Janssen-Cilag said that the leavepiece made the claim that olanzapine was simple to use and inferred a greater simplicity of use than its competitors. However, the SPC referred to the need for dosage adjustments in certain categories of patients and also stated that the dose needed to be adjusted up or down depending on clinical need. The presentation of Zyprexa's dosage and use as being "simple" was alleged to be overstated to the extent that it misled the reader. The Panel acknowledged that with Zyprexa many patients would require adjustment from the starting dose of 10mg. In the context of the dosage requirements for other antipsychotics, however, the Panel accepted that Zyprexa offered simplicity of use. Patients immediately received a therapeutic dose and did not need to be titrated slowly from a sub-therapeutic dose. No breach of the Code was ruled.

Janssen-Cilag alleged that the claim "One 10mg tablet is a therapeutic dose from day one" was misleading as it implied that efficacy with olanzapine was achieved on the first day of therapy. Further, the claim was misleading since it implied that the efficacy of olanzapine as shown in the leavepiece would be seen in the great majority of patients at the 10mg daily dose whereas studies showed the mean daily dose to be higher. The Panel noted that the page in question emphasised the use of a 10mg daily dose of Zyprexa. Although the legends of the graphs referred to doses of 5 to 20mg, the page in question gave emphasis only to 10mg. Given the number of patients who required a dose other than 10mg, the Panel considered the emphasis on 10mg to be misleading and in breach of the Code. Upon appeal by Lilly the Appeal Board noted that, according to the SPC, patients started with a dose of 10mg per day and that Lilly had data to suggest that the majority of patients were on 10mg per day. The claim might be interpreted as implying that efficacy was achieved on the first day of therapy but, on balance, the Appeal Board did not consider that the claim was misleading in that regard. The Appeal Board did not consider that there was over-emphasis of the 10mg dose. No breach of the Code was ruled.

Janssen-Cilag Ltd complained about a leavepiece (ref OL-86) for Zyprexa (olanzapine) which had been issued by Eli Lilly and Company Limited. The material included comparisons of Zyprexa with Janssen-Cilag's products haloperidol and risperidone.

1 Use of an asterisk against non-significant data

A boxed graph on page 2 of the leavepiece plotted the weekly improvement in positive symptoms over a six week period for Zyprexa and haloperidol. The lines diverged and at six weeks Zyprexa showed a greater improvement than haloperidol. The Zyprexa line had an asterisk next to it which referred to a figure at the bottom of the graph of p=0.117. Beneath the graph, and outside of the box, was the claim "At least as effective at improving positive symptoms as haloperidol".

COMPLAINT

Janssen-Cilag said that the graph showed two divergent lines and that an asterisk was used to denote a p value which was non-significant. On cursory inspection the divergent lines and inclusion of a p value gave the impression of a statistically significant difference between the compounds which in fact was not the case. Although Janssen-Cilag acknowledged that this was clarified in the text the company alleged that the visual presentation of the graph was misleading, in breach of Clause 7.6 of the Code.

RESPONSE

Lilly found it difficult to understand how the graph could be seen as misleading. The graph accurately portrayed the improvements in positive symptoms over the acute six week period of the study. It was precisely because the lines diverged beyond six weeks that Lilly considered it was necessary to draw attention to the fact that the difference was not statistically significant by adding an asterisk and footnote to make this clear. Lilly submitted that the graph was therefore not misleading.

PANEL RULING

The Panel noted that the single asterisk on the graph in question referred to a non-significant result. The Panel appreciated that the p value was given in a footnote but noted that no mention was made that the result was not statistically significant. The claim "At least as effective at improving positive symptoms as haloperidol" appeared beneath the graph. The Panel considered that, despite the footnote and the claim, the graph was visually misleading as its diverging lines gave the impression that there was a significant difference in efficacy between Zyprexa and haloperidol, in favour of Zyprexa, which was not so. In the Panel's view this impression might be reinforced by the use of an asterisk as some readers might assume that it was being employed to denote statistical significance and many would not read the footnote to discover that this was not the case. The Panel considered that a non significant result had been presented in a misleading way. A breach of Clause 7.6 of the Code was ruled.

2 Zyprexa starting dose of 15mg

On pages 3 and 4 of the leavepiece there were various claims of efficacy and safety for Zyprexa compared with risperidone. The claims were referenced to a comparative study by Tran *et al* (1996).

COMPLAINT

Janssen-Cilag said that it was clear from the Tran data that the starting dose for olanzapine used in the study was 15mg whereas the starting dose on the Zyprexa summary of product characteristics (SPC) was 10mg. The use of a starting dose that was higher than that licensed might alter the efficacy and safety information obtained on olanzapine versus what might be expected if the starting dose had been that licensed, ie 10mg. Janssen-Cilag said that nowhere in the leavepiece was this higher starting dose mentioned and the only reference to dosage was the claim that "10mg is a therapeutic starting dose". Janssen-Cilag considered that readers were led to believe that the efficacy/safety data reported versus risperidone was achieved at the usual 10mg starting dose for Zyprexa which was not the case. The company alleged that this misled the reader in breach of Clause 7.2.

RESPONSE

Lilly said that although it had not been made clear on pages 3 and 4 that a starting dose of 15mg Zyprexa had been used, this was not misleading for two reasons:

Firstly, the protocol allowed flexible titration of dose up or down in accordance with clinical need after week one of therapy. It was not possible to assume, therefore, that a starting dose of 15mg of Zyprexa determined the ongoing dose. Doses of Zyprexa would have varied up or down in individual patients during the course of the study within the dose range allowed. Patients treated with a starting dose of 10mg, within the same effective dose range recommended in the SPC, would be expected to have experienced Zyprexa dose adjustments according to clinical need in a similar way.

Secondly, in the company's studies to date, there was no data to show a significant difference in efficacy between doses of 10mg and 15mg of Zyprexa. A paper by Beasley *et al* (1996) was provided. It was hard to understand, therefore, how a starting dose of 15mg of Zyprexa could have significantly altered the measures of efficacy in this study relative to a starting dose of 10mg. With regard to safety outcomes, any increase in dose-dependent side effects associated with a starting dose of 15mg of Zyprexa rather than 10mg would have resulted in bias in favour of risperidone.

Lilly submitted that it was most unlikely that the starting dose of 15mg of Zyprexa used in the study resulted in a different outcome relative to the starting dose of 10mg recommended in the SPC. It was thus not necessary to include this information on these pages, and its omission did not mislead the reader. Lilly did not consider that the information presented on these pages represented a breach of Clause 7.2.

PANEL RULING

The Panel noted that pages three and four of the leavepiece detailed the results of the study by Tran *et al* in which the starting dose of Zyprexa 15mg had been subsequently adjusted within the range of 5 - 20mg/day. The recommended starting dose of Zyprexa was 10mg/day with a subsequent adjustment on the basis of individual clinical status within the range of 5 - 20mg/day (ref Zyprexa SPC). The Panel noted that the SPC also stated that "an increase to a dose greater than the routine therapeutic dose of 10mg/day, ie, to a dose of 15mg/day or greater, is recommended only after appropriate clinical reassessment". The Panel noted that while the graphs on pages three and four denoted the dose range of Zyprexa which had been used there was no mention of the higher than recommended starting dose.

Page five of the leavepiece summarised details of the dose and use of Zyprexa and in addition to a large visual of "10mg" there was the claim "One 10mg tablet is a therapeutic dose from day one". Thus the final page of the leavepiece prominently featured 10mg as a starting dose. Given the emphasis afforded to "10mg" as a starting dose on the final page the Panel considered that it was misleading not to have placed the preceding pages in the context of a starting dose of 15mg. Most readers would assume that Zyprexa had been used in the Tran study at its licensed starting dose which was not so. A breach of Clause 7.2 was ruled.

3 Simplicity of use

Page 5 of the leavepiece was headed "Zyprexa offers simplicity of use" followed by "simple dosage regimen". Three bullet points supported these headings. The bullet points were "One 10mg tablet is a therapeutic dose from day one", "Additional flexibility of dose range between 5 and 20mg" and "Initial titration period is unnecessary - unlike sertindole, risperidone and many typical antipsychotics". The bullet points were followed by the statement "No requirement for routine physiological testing with Zyprexa". At the bottom of the page, and taking up almost a quarter of it, was a visual which showed the figure "10mg" in relief.

COMPLAINT

Janssen-Cilag said that the leavepiece made the claim that olanzapine was simple to use and inferred a greater simplicity of use versus its competitors. However the current SPC for Zyprexa advised consideration of starting dosage adjustments in women, non-smokers, the elderly and those with renal or hepatic impairment and also stated that the dose needed to be adjusted up or down depending on clinical need. Indeed, the SPC recommended a starting dose of 10mg but as shown in point 4 below, in a study involving 1,336 olanzapine-treated patients, 78% of subjects were titrated to doses other than 10mg. Janssen-Cilag alleged that the presentation of olanzapine's dosage regimen and its use as being "simple" was overstated to the extent that it misled the reader and was in breach of Clause 7.2.

RESPONSE

Lilly said that any claim should be considered in the context within which it was presented. In this case, the term "simplicity of use" was not intended to be an unqualified statement, but rather it clearly referred to the specific attributes of Zyprexa listed immediately below it.

These attributes comprised: the almost unique convenience of a starting dose of 10mg which was described as a therapeutic dose in the SPC; the lack of any recommended period of titration on initiating therapy; and the lack of any requirement for routine physiological testing.

These attributes represented clear, clinically significant differences between Zyprexa and other antipsychotics, especially other atypical antipsychotics such as risperidone, sertindole, and clozapine. Within this context, they justified the claim "simplicity of use".

Lilly said that there were, in addition, other justifications for the claim "simplicity of use", notably the fact that Zyprexa was administered as a single daily dose, without regard to meals, and had a low potential for drug-drug interactions.

Lilly noted that the complaint referred to a study in which 78% of patients treated within a dose range of 5 - 20mg of Zyprexa were titrated to doses other than 10mg. Lilly submitted that detailed examination of the data revealed that only 50% of patients were actually treated with doses of Zyprexa greater than 10mg. The availability of a licensed dose range of 5 - 20mg of Zyprexa was made clear in the piece, thus acknowledging that a proportion of patients might be treated at doses other than 10mg at the discretion of the treating physician. Given the refractory nature of schizophrenia, and the pragmatic approach to treatment which resulted, this situation was likely despite the company's data which suggested no significant difference in efficacy between doses of 10mg and 15mg of Zyprexa.

Lilly said that in any case, it was not claimed in the leavepiece that 10mg of Zyprexa was likely to be the most commonly used dose, rather that the starting dose of Zyprexa was a therapeutic dose and thus contributed to its "simplicity of use". It had clearly been established in a fixed dose trial that 10mg of Zyprexa was an effective dose, and this was reflected in the wording of the SPC: "The recommended starting dose for olanzapine is 10mg/day....increase to a dose greater than the routine therapeutic dose of 10mg....is recommended only after appropriate clinical reassessment".

Lilly said that the complaint implied that the Zyprexa SPC recommendation for consideration of starting dose adjustments in certain patient groups, and the availability of a dose range of 5 - 20mg, represented disadvantages of Zyprexa which rendered the claim "simplicity of use" misleading.

Regarding the dose range of 5 - 20mg, if the possibility of varying the dose within a certain range was unique to Zyprexa, this could perhaps be seen to represent a disadvantage. In fact, in this respect Zyprexa did not differ from almost all other antipsychotics. The availability of a dose range could thus hardly be seen as sufficient disadvantage as to render the claim "simplicity of use" invalid. Moreover, the availability of the dose range was made clearly explicit directly below the statement referring to the starting dose.

Lilly said that with regard to the advice given in the Zyprexa SPC to consider a lower starting dose in certain patient groups, it was worth noting that a lower starting dose of Zyprexa was not a requirement or recommendation for any patient subgroup. This represented an advantage relative to many other antipsychotics. For example, the risperidone SPC recommended the use of a starting dose in the elderly, or in patients with compromised renal or hepatic function, which was half the usual adult starting dose. This might subsequently be titrated upwards only to a dose equal to a maximum of half the usual adult maintenance dose. The advice given in the Zyprexa SPC did not therefore represent a disadvantage of Zyprexa sufficient to compromise the validity of the claim "simplicity of use".

The scope of the claim "simplicity of use", therefore, was clearly defined and justifiable, and was not compromised in any way by the dose range of Zyprexa, or the advice to consider a lower starting dose in certain patient groups. The claim was therefore not misleading and did not represent a breach of Clause 7.2.

PANEL RULING

The Panel noted that the page in question positioned Zyprexa against other antipsychotics, in particular sertindole, risperidone and clozapine. With regard to dosing the Panel noted that the starting dose of Zyprexa was 10mg/day with subsequent adjustment within the range of 5 - 20mg/day. The dose for risperidone was 2mg/day with a three day titration period to 6mg/day. The usual optimal dose lay between 4 - 8mg/day. The starting dose for sertindole was 4mg/day which could be increased every 3 - 4 days by 4mg/day to the usual daily maintenance dose of 12 - 20mg/day. The starting dose for clozapine was 12.5mg once or twice a day which should be titrated slowly to 300mg/day within 2 - 3 weeks. Most patients responded to 200 - 450mg/day in divided doses. The Panel noted that the initial dose of Zyprexa (10mg) lay within the therapeutic dosage range. The initial doses of risperidone, sertindole and clozapine all lay below the expected therapeutic dose ranges.

With regard to certain patient groups such as the elderly, the renally impaired, reduced hepatic function etc, the

Panel noted that all four products, Zyprexa, sertindole, risperidone and clozapine had special dosage instructions, with such patients usually starting on smaller doses with a slower adjustment to the final dose. The Panel considered that in terms of such patients Zyprexa was no more difficult to use than the other antipsychotics.

The Panel acknowledged that with Zyprexa many patients would require dose adjustment from the initial starting dose of 10mg. Data from Tollefson *et al* (see point 4 below) suggested that only 22% of patients would stay on 10mg/day. In the context of the dosage requirements for other antipsychotics, however, the Panel accepted that Zyprexa offered simplicity of use. Patients immediately received a therapeutic dose, the dose of Zyprexa did not need to be titrated slowly over time from a sub-therapeutic starting dose. No breach of Clause 7.2 was ruled.

4 Claim "One 10mg tablet is a therapeutic dose from day one."

COMPLAINT

Janssen-Cilag said that the claim "One 10mg tablet is a therapeutic dose from day one" was misleading since it implied that efficacy with olanzapine was achieved on the first day of therapy. Further, the olanzapine daily doses used in the comparative studies with haloperidol and risperidone were represented as a range and shown as "5 - 20mg" on pages 2 and 4. Tollefson *et al* (1997) reported a comparative study with 1,336 olanzapine treated patients and 660 haloperidol treated subjects. The mean modal dose of olanzapine was 13.2mg per day. The distribution of modal daily doses of olanzapine was: 5mg-28%, 10mg-22%, 15mg-19% and 20mg-31%. In the Tran study, which compared olanzapine and risperidone, the mean modal daily dose of olanzapine was 16.9mg at week 8 and 17.1mg at week 28. Janssen-Cilag alleged that the claim was further misleading since it implied that the efficacy of olanzapine as demonstrated in the piece on pages 2 and 4 was expected to be seen in the great majority of patients at the 10mg daily dose. A breach of Clause 7.2 of the Code was alleged.

RESPONSE

Lilly submitted that the leavepiece neither stated nor implied that 10mg of Zyprexa either began to treat symptoms at day one or that patients would have responded at day one. It merely stated that a proven therapeutic dose of 10mg could be started on day one in contrast to the mandatory titration requirements of many other antipsychotics. Lilly said that it was made completely clear throughout that the efficacy and data shown in the piece referred to a dose range of 5 - 20mg of Zyprexa rather than to a fixed dose of 10mg.

Lilly said that every single data series on every single graph stated clearly the dose range of each drug used in the studies represented. It was not claimed or implied anywhere in the piece that the "great majority" of patients would exhibit efficacy at 10mg/day. It was merely claimed, as described above, that a dose of 10mg of Zyprexa was "a" and not "the" therapeutic dose which might be given from day one of therapy. This dose had been established in a fixed dose study to have superior efficacy to placebo. This was recognised in the SPC which described 10mg of Zyprexa as a "routine therapeutic dose".

Lilly contended that the claim "one 10mg tablet is a therapeutic dose from day one" was therefore not misleading and did not represent a breach of Clause 7.2

PANEL RULING

The Panel noted that page five of the leavepiece included the claim "One 10mg tablet is a therapeutic dose from day one" as well as a large visual of "10mg". The Panel considered that the page emphasised the use of a 10mg dose of Zyprexa.

The Panel noted that the Tollefson data showed that 78% of patients on Zyprexa required a dose other than 10mg. The Tran data had shown that after 28 weeks of treatment the mean modal dose of Zyprexa was 17.1mg suggesting that many patients were on a dose of greater than 10mg. The Panel noted that although the legends of the graphs in the leavepiece referred to a dose of 5 - 20mg the final page gave emphasis to only 10mg. Given the number of patients who required a dose other than 10mg the Panel considered the emphasis on only a 10mg dose to be misleading, in breach of Clause 7.2 of the Code.

APPEAL BY LILLY

Lilly said that the claim did not imply that efficacy was achieved on the first day of therapy. The claim was simply making it clear that patients could be started on a dose that had proven therapeutic effect from day one. In other words, the patient did not need to be titrated up from doses which had no therapeutic effect to a dose which did have a therapeutic effect.

It clearly stated in the SPC that 10mg/day was the "routine therapeutic dose" and that it was a "starting dose". It could not therefore be misleading to state that 10mg was a therapeutic dose from day one when this was clearly what the SPC stated. In a fixed dose study 10mg was shown to have superior efficacy to placebo. The two studies referred to (ie, Tollefson *et al* and Tran *et al*) were dose-ranging studies carried out prior to it being known what the therapeutic dose for Zyprexa was.

The claim did not imply that the efficacy as seen in the leavepiece would be seen at 10mg in the "great majority of patients". Where specific efficacy claims were made on other pages in the leavepiece it was clearly stated that the dose ranges used were 5-20mg. These claims were not repeated here.

As 10mg/day was, in accordance with the SPC, a "routine therapeutic dose" and a "starting dose", it was not misleading to include a visual of 10mg on this page. This was the amount that physicians were recommended to prescribe as their starting dose. It did not mean that they could not increase the dose at a later stage if in their judgement the patient's situation required such an increase. The "emphasis" on 10mg was simply that this was the dose which physicians would, at least initially, use. This was particularly emphasised as it was in contrast to their normal clinical experience with antipsychotics ie, titrating up to a therapeutic dose from a

starting dose. As stated in the SPC, only after "appropriate clinical reassessment" should the dose of Zyprexa be increased. Many patients would respond to 10mg. The fact that doses were subsequently increased did not affect the fact that 10mg was a therapeutic dose and could be taken from day one.

The statement did not state or imply that the efficacy referred to on previous pages of the leavepiece would be achieved at 10mg in every patient. On the pages in question it was clear within which dosage range the results were achieved. The piece was not misleading.

Lilly provided copies of the Psychotrak Survey for olanzapine (Hospital Marketing Services Limited) which analysed all prescriptions where a dosage was given, including new initiations, dosage titrations and repeat therapy. According to the January and May 1997 runs of Psychotrak, 84.2% and 53.2% (respectively) of patients were on 10mg/day. Review of the proportion of repeat prescriptions where the dose was unchanged showed 10mg to be the most likely maintenance dose currently used (5mg 7.3%, 10mg 63.4%, 15mg 17.1%). This suggested that, in fact, the majority of patients on Zyprexa were on 10mg/day.

The company pointed out that the leavepiece was intended for psychiatrists. Different material was used with GPs. The intended audience would not believe that clinical efficacy would be seen from day one. It was important to take the page in context. No efficacy claims were made.

APPEAL BOARD RULING

The Appeal Board noted that the SPC for Zyprexa (olanzapine) stated:

"The recommended starting dose for olanzapine is 10mg/day, administered as a single daily dose without regard to meals. Daily dosage may subsequently be adjusted on the basis of individual clinical status within the range of 5-20mg daily. An increase to a dose greater than the routine therapeutic dose of 10mg/day, ie, to a dose of 15mg/day or greater, is recommended only after appropriate clinical reassessment."

The Appeal Board examined the page in question which was headed "Zyprexa offers simplicity of use". This was followed by a claim "Simple dosage regimen" followed by the claim at issue, beneath which appeared two further claims "Additional flexibility of dose range between 5-20mg" and " Initial titration period is unnecessary - unlike sertindole, risperidone and many typical antipsychotics".

The Appeal Board noted that patients being treated with Zyprexa started with a dose of 10mg per day according to the SPC and the company had data to suggest that the majority of patients were on a dose of 10mg per day. The Appeal Board noted that the claim in question might be interpreted as implying that efficacy was achieved on the first day of therapy. On balance, however, the Appeal Board did not consider that the claim was misleading with regard to the allegation that it implied that efficacy was achieved on the first day of therapy and no breach of Clause 7.2 was ruled. The Appeal Board did not consider there was over-emphasis of the 10mg dose and therefore ruled no breach of Clause 7.2 of the Code.

The appeal was therefore successful.

Complaint received **24 July 1997**

Case completed **9 December 1997**

CASE AUTH/588/7/97

SMITHKLINE BEECHAM v LILLY

Prozac leavepiece

SmithKline Beecham submitted a complaint regarding a Prozac leavepiece issued by Eli Lilly. The complaint concerned a chart comparing Prozac and paroxetine whereby a number of benefits were listed followed by a tick or a cross in the adjacent columns headed 'Prozac' and 'paroxetine'.

The Panel considered that the cross given in the paroxetine column in relation to the statement "20mg dose recommended for ALL patients (as data sheet)" which appeared beneath a heading "Initiating Therapy" was incorrect as the recommending starting dose for paroxetine was 20mg per day. The Panel also considered that placing a tick for Prozac next to the statement "20mg dose recommended for ALL patients (as data sheet)" was misleading as the data sheet recommended a lower dose for certain patients. Breaches of the Code were ruled.

A statement "Benefit of extended half life during therapy" attributed to Prozac was ruled to be in breach as it would be interpreted as meaning that when Prozac was taken at its licensed frequency and dosage its extended half life was beneficial, and this is not necessarily so.

The Panel ruled no breach of the Code with regard to a section headed "Cessation of therapy" and the related benefit "No data sheet recommendation for tapering" which was followed by a tick for Prozac and a cross for paroxetine. There was no data sheet recommendation for tapering for Prozac whereas there was such a recommendation for paroxetine.

SmithKline Beecham Pharmaceuticals UK submitted a complaint about the promotion of Prozac (fluoxetine) by Eli Lilly and Company Limited. The complaint concerned a leavepiece (ref PZ/912) entitled "Why choose Prozac above paroxetine?". A page entitled "The benefits of Prozac in the treatment of depression" compared Prozac and paroxetine (SmithKline Beecham's product, Seroxat) under three main headings: "Initiating Therapy", "Maintaining Therapy" and "Cessation of Therapy". Underneath each heading were listed a number of relevant product benefits. For each benefit listed either a tick or a cross appeared in the adjacent columns marked 'Prozac' and 'Paroxetine'.

1 Heading "Initiating Therapy", related benefit "20mg dose recommended for ALL patients (as data sheet)"

The columns adjacent to the stated benefit contained a tick for Prozac and a cross for paroxetine.

COMPLAINT

SmithKline Beecham noted that this benefit referred to the initiation of treatment for depression only. SmithKline Beecham pointed out that the recommended starting dose of Seroxat (paroxetine) for the treatment of depression in adults was 20mg per day. In elderly patients or those with renal or hepatic impairment it was also recommended that a starting dose of 20mg was used. SmithKline Beecham therefore submitted that 20mg was the recommended starting dose of paroxetine for the treatment of all patients with depression and therefore the cross given for paroxetine in relation to this statement was incorrect.

SmithKline Beecham alleged that fluoxetine (Prozac) did not have a 20mg starting dose for all patients. The data sheet stated that fluoxetine was extensively metabolised by the liver and excreted by the kidneys. A lower dose was therefore recommended for those patients with significant hepatic dysfunction or mild to moderate renal failure. SmithKline Beecham alleged that the statement was therefore misleading, in breach of Clause 7.2.

RESPONSE

Lilly submitted that the statement was referenced to the Prozac data sheet and the paroxetine data sheet in the ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1996-97. The statement referred to the benefit of a simpler regime of initiating treatment with Prozac compared with paroxetine and was not misleading. Simpler medication regimes were associated with better patient compliance (Sanson-Fisher and Clover (1995)). Lilly noted a suggestion that upward dose titration of specific serotonin reuptake inhibitors (SSRIs) might prolong the time taken to achieve a clinical response (Donoghue (1996)).

Lilly submitted that a fair comparison between Prozac and paroxetine upon the initiation of therapy could only be made if the term "initiating therapy" was taken to include the period of exposure up to the stage of achieving a clinically effective dose.

Lilly noted that the recommendation in the Prozac data sheet was for a dose of 20mg per day for adults and the elderly and that there was no recommendation for any increase in this dose in any patient with depression. In contrast, Lilly noted that whilst the paroxetine data sheet recommended a dose of 20mg per day it advised that "In some patients it may be necessary to increase the dose. This should be done gradually by 10mg increments to a maximum of 50mg according to the patient's response". With regard to elderly patients the paroxetine data sheet also recommended a dose of 20mg per day and stated that "In some patients it may be necessary to increase the dose This should be done gradually by 10mg increments to a maximum of 40mg according to the patient's response". Lilly therefore submitted that the licensed recommendations for the use of Prozac and paroxetine in the initiation of therapy, to the stage of achieving a clinically effective dose, were different. A 20mg dose of Prozac was recommended for all patients. No dose titration was required. The data sheet recommendation was that some patients receiving paroxetine would require doses higher than 20mg.

Lilly noted that in the Donoghue study (1996), 21.1% of prescriptions for paroxetine were for greater than 20mg

compared to 6.8% of Prozac prescriptions, suggesting that the requirement for increased doses of paroxetine was a significant issue in practice.

Lilly acknowledged that the Prozac data sheet stated that "Fluoxetine is extensively metabolised by the liver and excreted by the kidneys. A lower dose, eg. alternate day dosing, is recommended in patients with significant hepatic dysfunction or mild to moderate renal failure (GFR 10-50ml/minute)". Lilly submitted that the statement at issue intended to address the issue of no recommendation for dose titration for Prozac compared to a recommendation for dose titration for some patients with paroxetine. Lilly submitted that the statement at issue was consistent with the data sheet recommendation for patients with significant hepatic impairment or mild to moderate renal failure. The recommendation for these patients was to use a 20mg dose on alternate days. The long half-life of the compound permitted alternate day dosing to achieve a therapeutic dose without resulting in major fluctuations in serum levels. This was consistent with the principle of using a single dose of 20mg of Prozac and not requiring various strengths of preparation which added potential complexity for patient and prescriber.

PANEL RULING

The Panel examined the data sheet for paroxetine and noted that the recommended starting dose was 20mg per day. The recommendation provided for upward dose titration of paroxetine in some patients dependent upon response. A starting dose of 20mg per day was also recommended for patients with renal or hepatic impairment and for elderly patients.

The Panel noted that by common usage "Initiating therapy" meant commencing or starting therapy. It did not extend beyond the commencement of a dosage regime to the point in time when that dose became clinically effective. The Panel considered that although upward dose titration of paroxetine might be an issue in some patients, 20mg was the recommended starting dose for all patients. The statement at issue appeared in a section headed "Initiating Therapy". The Panel considered that the cross given for paroxetine in relation to the statement "20mg dose recommended for ALL patients (as data sheet)" was incorrect. The Panel therefore ruled a breach of Clause 7.2 of the Code.

The Panel examined the Prozac data sheet and noted that while 20mg per day was the recommended starting dose for patients with depression the data sheet did recommend a lower dose, for example alternate day dosing, in patients with significant hepatic dysfunction or mild to moderate renal failure. The Panel noted the emphasis given to the word "all" in the statement by the use of capital letters. The statement implied that the universally recommended starting dose was 20mg per day. It would not be interpreted as meaning that the universal dose was 20mg but that some patients would take it every day whereas others would only take it every other day. The Panel considered that placing a tick for Prozac next to the statement "20mg dose recommended for ALL patients (as data sheet)" was misleading. It therefore ruled a breach of Clause 7.2 of the Code.

2 Section headed "Maintaining Therapy", related benefit "Benefit of extended half life during therapy"

The stated benefit was followed by an asterisk. The explanation for the asterisk, given by way of a footnote at the bottom of the page, was "An extended half life may be less likely to precipitate discontinuation symptoms on discontinuation of antidepressant therapy, or result in relapse if doses are missed. The half-life should be borne in mind if stopping Prozac or starting other treatment." The stated benefit was followed by a tick in the Prozac column and a cross in the paroxetine column.

COMPLAINT

SmithKline Beecham pointed out that the half life was of limited importance during treatment, and both products were licensed as once daily therapies. Taken at the licensed dose and frequency there was no benefit from an extended half life. An extended half life could be detrimental if the patient developed an adverse reaction and therapy had to be withdrawn.

SmithKline Beecham noted that the data sheet for fluoxetine emphasised the need for the long half life to be "borne in mind when stopping or starting treatment" or when "considering pharmacodynamic or pharmacokinetic drug interactions". SmithKline Beecham pointed out that the extended half life did not always mean a "benefit" to the patient. The statement was therefore misleading in breach of Clause 7.2 of the Code.

RESPONSE

Lilly pointed out that the footnote had been amended following discussions between SmithKline Beecham and Lilly to ensure that it was consistent with the Prozac data sheet.

Lilly submitted that the benefit of the extended half life was referenced to Stokes (1993). In the company's view it was precisely because of the fact that medication was often not taken at the licensed dose and frequency that the extended half life was an advantage during maintenance therapy. Lilly noted that it was estimated that a third of patients delay or omit many prescribed doses of medication independent of drug, disease, prognosis or symptoms (Urquhart (1996)). In these circumstances a pharmaceutical agent with a duration of action appreciably longer than the prescribed interval between doses was therapeutically important and might be a crucial element in achieving the best outcome. To support this argument Lilly referred to data on file, a copy of which was provided to the Panel, which suggested that even when compliance appeared to be good, the majority of patients would miss several doses. Lilly referred to a further double blind study by Blomgren *et al* (1997), where patients on SSRIs had interruptions of their medication for periods of 5 to 8 days during which placebo was substituted. During periods of SSRI interruption patients on paroxetine experienced significantly more discontinuation symptoms and worsening of depression scores than patients on fluoxetine.

Lilly submitted that it had not made the claim that the extended half life always meant a benefit to the patient. The statement referred to the benefits of the extended half

life in maintaining therapy because of a lower likelihood of discontinuation symptoms or relapse resulting from missed doses.

PANEL RULING

The Panel noted the view of SmithKline Beecham that if Prozac was taken at the licensed dose and frequency there was no benefit from an extended half life. The Panel noted that the statement had been qualified by the footnote "an extended half-life may be less likely to precipitate discontinuation symptoms on discontinuation of anti-depressant therapy or result in relapse if doses are missed. The half-life should be borne in mind if stopping Prozac or starting other therapy.". The Panel noted that whilst the footnote sought to qualify the statement at issue it was a well known principle under the Code that material could not be qualified by the use of a footnote.

The Panel noted the data provided by Lilly, some of which, namely the data on file, was not to be passed to SmithKline Beecham. The Panel accepted that the extended half life might be of benefit to patients when doses were missed. However the statement would be interpreted as meaning that an extended half life was beneficial when Prozac was taken at its licensed frequency and dosage. This was not necessarily so. The Panel considered the statement was misleading and ruled a breach of Clause 7.2 of the Code.

3 Section headed "Cessation of Therapy", related benefit "No data sheet recommendation for tapering"

The columns adjacent to the stated benefit contained a tick for Prozac and a cross for paroxetine.

COMPLAINT

SmithKline Beecham noted that whilst the statement was true for Prozac, the British National Formulary recommended that antidepressants in general should be withdrawn gradually, "over a period of about 4 weeks". SmithKline Beecham submitted that gradual withdrawal of antidepressant medication was considered good clinical practice and should not be viewed as a disadvantage peculiar to paroxetine. The statement was alleged to be misleading in breach of Clause 7.2 of the Code.

RESPONSE

Lilly noted that the Committee on Safety of Medicines had received more reports of symptoms occurring on withdrawal of paroxetine than with other SSRIs (CSM (1993), Young and Ashton (1996)). The long half life of fluoxetine, compared to paroxetine, made the compounds different with regard to the rate of the fall of serum levels on cessation. A gradual tapering of dose was not required on cessation of therapy with fluoxetine. A randomised placebo controlled study by Michelson *et al* (1997) showed that clinically significant withdrawal symptoms did not occur after abrupt substitution of placebo for fluoxetine compared to continuing the fluoxetine. Coupland *et al* (1996) reported the rates of symptoms experienced in 171 outpatient clinic attendees who were supervised during antidepressant tapering and discontinuation. 20% of patients on paroxetine experienced at least one new symptom during discontinuation compared with none of those patients who had been prescribed fluoxetine.

Lilly submitted that the consensus of current research was that despite the general advice regarding discontinuation of antidepressant therapy given in the BNF, tapering of dose was not required on cessation of therapy with Prozac. This, submitted Lilly, did indeed confer a significant benefit of Prozac compared to paroxetine since it lowered the risk of discontinuation symptoms, provided ease of use and required simpler instructions to patients.

PANEL RULING

The Panel noted that the data sheet for Prozac did not contain any recommendation for tapering when therapy was stopped. The data sheet stated that "When dosing is stopped, active drug substances will persist in the body for weeks. This should be borne in mind when starting or stopping treatment".

The Panel noted that the data sheet for paroxetine stated that symptoms had been reported upon abrupt discontinuation and "...it is therefore recommended that when antidepressant treatment is no longer required, gradual discontinuation by dose-tapering or alternate day dosing be considered".

The Panel noted that the British National Formulary (March 1997) stated that, if possible, SSRIs should be withdrawn slowly. The BNF entry for paroxetine included a section "CSM advice: Extrapyramidal reactions (including orofacial dystonias) and withdrawal syndrome are reported to the CSM more commonly than with other SSRIs".

The Panel noted that although the BNF recommended that SSRIs were slowly withdrawn, the statement at issue "No data sheet recommendation for tapering" was correct for Prozac. There was no data sheet recommendation for tapering for Prozac whereas there was such a recommendation for paroxetine. The Panel therefore ruled no breach of the Code.

Complaint received **25 July 1997**

Case completed **15 October 1997**

CASE AUTH/589/7/97

NO BREACH OF THE CODE

LEO v MERCK PHARMACEUTICALS

Curatoderm promotional item

Leo Pharmaceuticals complained about a Curatoderm promotional item issued by Merck Pharmaceuticals, alleging that the paper cited in the item did not include data to support the statement that Curatoderm was "Well tolerated - even in facial and flexural psoriasis". The paper did not state the number of patients with flexural psoriasis who were treated with Curatoderm and it was therefore not possible to draw any conclusions in respect of the tolerance of patients with flexural psoriasis.

The Panel considered that whilst the cited reference did not completely substantiate the claim, it was relevant as patients in the study were permitted to treat both facial and flexural psoriasis. The Panel considered that additional data provided by Merck read in conjunction with the cited paper did support the claim and ruled no breach of the Code.

Upon appeal by Leo, the Appeal Board noted that the SPC for Curatoderm did not contain any precautions regarding the use of the product on flexures. In the Appeal Board's view, when considered overall, the data provided by Merck was sufficient to substantiate the claim. The Appeal Board upheld the Panel's ruling that there had been no breach of the Code.

Leo Pharmaceuticals complained about a Curatoderm promotional item, dated 8 August 1996, distributed by Merck Pharmaceuticals. The promotional item was an A5 card to which a branded pen could be attached. It was given to doctors attending the Merck stand at the British Association of Dermatologists' meeting, Summer 1997, and could also be used by representatives when visiting doctors. The claim at issue was that Curatoderm was "Well tolerated - even in facial and flexural psoriasis", referenced to a paper by Van de Kerkhof *et al* (1996).

COMPLAINT

Leo alleged that the paper cited did not include data to support the statement that Curatoderm was "Well tolerated - even in facial and flexural psoriasis". The paper did not state the number of patients with flexural psoriasis in the study who were treated with Curatoderm. It was not possible therefore to draw any conclusion in respect of the tolerance of patients with flexural psoriasis. The complainant alleged a breach of Clauses 7.2, 7.3 and 7.7 of the Code.

RESPONSE

Merck Pharmaceuticals submitted that the claim was fair, accurate and balanced. It was based on an up-to-date evaluation of all the evidence and was capable of substantiation.

Merck submitted that clinicians were aware that the difficult to treat and often restricted areas in psoriasis were the face and flexures. The claim "even on the face and flexures" made it clear that Curatoderm was not restricted from these difficult areas on the grounds of safety. Merck referred to a previous case (Case AUTH/400/2/96) in which there appeared to be no case to answer in respect of reference to these specific problem areas of skin.

Merck submitted that there were no precautions listed in the summary of product characteristics (SPC) regarding these areas and it was obvious to prescribers that the product could be used in these areas without expecting any significant difference in tolerability compared to the rest of the body (excluding the scalp). Merck pointed out that facial application was specifically referred to in the SPC and supported by data in the paper by Van de Kerkhof *et al*. Merck submitted that it was generally accepted that facial skin tolerance predicted that seen in the flexures, both areas being seen as "sensitive" (Chu (1996)). Merck stated that clinical trials conducted with Curatoderm, did not exclude patients with psoriasis at flexural sites. Unfortunately the exact sites were not recorded as such at the time of the trials but flexural psoriasis was a feature in around 20% of patients with the disease (Poyner and Fell (1995)). Thus tolerance data collected in such trials related to these areas as well as the rest of the body (excluding the scalp).

Merck referred to a review of the spontaneously reported adverse reaction database which showed that the total number of local skin reactions, ranging from itching to deterioration of the disease, reported on Curatoderm in the UK, Germany and Switzerland since the launch of the product amounted to 72 cases from a conservatively estimated total exposure to 60,000 plus patients (calculated from sales data). Thus even if all these skin reactions had been associated with flexural psoriasis (about 20% of patients) it would still represent an incidence of less than 1% (6 in 1000). It was therefore justifiable to use the term "well tolerated".

PANEL RULING

The Panel noted that the cited reference did not provide any details about the actual number of patients in the study who had flexural psoriasis. The test lesions were, according to the study, predominantly localised on arms and/or legs, but in a quarter of all patients (24.6%) test lesions were localised on the face or on the face plus other parts of the body. Patients were permitted to treat both facial and flexural psoriasis which, according to the authors, were areas that were relatively susceptible to irritation with vitamin D_3 analogues. The Panel noted that 15 of the 122 intention-to-treat patients (12.3%) reported one or more symptoms of skin irritation. Only one of the 15 patients discontinued treatment of the irritated lesion. The authors noted that "It was possible that the irritations were related to the study medication. Nevertheless they did not occur more frequently in the tacalcitol-treated areas than in the placebo-treated lesions". The placebo treatment was the base without active substance. Of the 30 patients whose test areas were localised on the face, only two reported symptoms of local irritation there.

The Panel noted Merck's submission that flexural psoriasis was present in around 20% of patients with the disease (Poyner and Fell). The Panel assumed that the precise figure was 21.3% which it calculated from a table which showed that 78.7% of patients in the study did not have psoriasis present on the flexures. The Panel noted the submission that it was generally accepted that facial skin tolerance predicted that seen in the flexures. Both areas being seen as sensitive. The Panel noted that the Chu paper, which was a review of the efficacy, side effects and place in therapy of tacalcitol, referred to a study by Gerritsen *et al* in 58 psoriasis patients treated for between six and twelve months. Patients were allowed to treat the entire body including face and flexures. Eight of the 58 patients experienced skin irritation or burning irritation although no patient discontinued treatment for this reason. The Chu review concluded that tacalcitol was a well tolerated treatment even when applied to lesions at sensitive sites such as the face and flexures. The Panel noted that the reporting rate of adverse reactions did not reflect the actual level of side effects associated with the product.

The Panel noted that whilst a reference given in promotional material should be relevant to the claim being made, the given reference did not have to completely substantiate the claim. It was possible to use additional material to substantiate the claim.

The Panel considered that whilst the cited reference did not completely substantiate the claim that Curatoderm was "Well tolerated even in .... flexural psoriasis" it was relevant as patients in the study were permitted to treat both facial and flexural psoriasis. The Panel considered that the additional data provided by Merck when read in conjunction with the cited reference did support the claim that Curatoderm was "Well tolerated - even in facial and flexural psoriasis". The Panel therefore ruled no breach of the Code.

APPEAL BY LEO

Leo said that it must first of all be emphasised that its complaint related to the lack of ability to substantiate the claim that Curatoderm was "well tolerated ... in flexural psoriasis", this claim being referenced to a paper by Van de Kerkhof *et al* (1996). Leo had not challenged the claim in respect of tolerance in facial psoriasis and it believed that tolerance data in facial psoriasis could not necessarily be extrapolated to a claim of tolerance in flexural psoriasis.

Leo noted the Panel's views as follows:

"The Panel noted that the cited reference did not provide any details about the actual number of patients in the study who had flexural psoriasis. The test lesions were, according to the study, predominantly localised on arms and/or legs but in a quarter of all patients (24.6%) test lesions were localised on the face or on the face plus other parts of the body"

and also

"the Panel noted Merck's submission that flexural psoriasis was present in around 20% of patients with the disease (Poyner and Fell). The Panel assumed that the precise figure was 21.3% which it calculated from a table which showed that 78.7% of patients in the study did not have psoriasis present on the flexures".

Although it might be concluded that around 20% of patients had flexural psoriasis and although it was permitted to treat the flexural areas in the Van de Kerkhof study referenced by Merck, Leo agreed with the Panel that the cited reference did not provide any details about the actual number of patients in the study with flexural psoriasis. It was not permissible to assume that a significant number of patients were treated for flexural psoriasis in the Van de Kerkhof paper and it was certainly not acceptable to assume that, if any patients were treated, then the drug was well tolerated.

Sub-set analysis within a clinical trial could of itself be misleading. Before any claim in respect of a sub-set within a clinical trial could be made, then this sub-set should be carefully analysed and if to be the subject of a promotional claim, should have statistical validity.

Leo noted the comment by Merck that the exact sites treated were not recorded at the time of the trials and Leo suggested, therefore, that claims of tolerance for any particular sub-set of patients or for any particular anatomical site could not be made.

Leo challenged the Panel's statement "The Panel noted the submission that it was generally accepted that facial skin tolerance predicted that seen in the flexures." and pointed out an internal contradiction within the reply from Merck. In the Merck reply, the statement was made on the one hand that it was obvious to prescribers that the product could be used in these areas without expecting any significant difference in tolerability compared to the rest of the body (excluding the scalp) whilst, at the same time, stating that "it is generally accepted that facial skin tolerance predicted that seen in the flexures, both areas being seen as "sensitive"".

Leo referred to the Panel's view that:

"The Panel noted that the Chu paper, which was a review of efficacy, side effects and place in therapy of tacalcitol, referred to a study by Gerritsen *et al* in 58 psoriasis patients treated for between six and twelve months. Patients were allowed to treat the entire body including face and flexures".

The study by Gerritsen *et al* had not been made available to Leo. The reference given was to an abstract of the Third European Symposium Scientific Meeting for Dermatologists, Hamburg 1995, which Leo believed might have been a closed meeting. The opinion of Chu in his review of tacalcitol in Prescriber (October 1996) was not relevant to this claim, since no data were included in the review in respect of the claim "well tolerated in flexural psoriasis".

In Leo's view significant emphasis had been given by the Panel to these data. The Gerritsen publication was not included in the material forwarded to Leo from the Panel and was not available on request. It appeared that, despite the results of this publication forming a pivotal part of the ruling, these data had not been reviewed by the Panel. It was impossible for Leo to make any comment in respect of the Gerritsen publication but it was surprised that these data were not reviewed at the time when the complaint was considered.

Leo noted that references used in promotional material

did not have to substantiate the claim. It knew that it was possible for additional material to be made available to substantiate the claim. No such data were available to Leo.

RESPONSE FROM MERCK

Merck did not understand Leo's comments regarding "the Gerritsen paper"; this was not quoted in any of Merck's correspondence and the Chu review was included to indicate that it was currently held opinion that both the face and flexures were perceived as "sensitive" areas of the skin.

Merck realised that it might have included additional reported ADRs in the original analysis of safety/tolerability that were not strictly related to the skin, such as "hair discolouration". A further review of the spontaneously reported adverse reaction database up to 31 May 1997, showed that the total number of local skin reactions, ranging from "itching" to "deterioration of disease", reported on Curatoderm in the UK, Germany and Switzerland since launch amounted to 69 cases from a conservatively estimated total exposure to 60,000 plus patients (calculated from sales data). Merck supplied copies of the database listing together with an in-house document which explained the conservative basis for the probable number of patients exposed. Thus even if all these skin reactions had been associated with flexural psoriasis (about 20% of patients), it would still represent an incidence of less than 1% (approximately 6 in 1000). It was therefore justifiable to use the term "Well tolerated".

FURTHER COMMENTS FROM LEO

Leo said that it was clear from the response given by Merck that it still did not understand that a promotional claim in a particular indication must be capable of substantiation by data generated in that indication. There was no evidence for the claim in flexural psoriasis.

APPEAL BOARD RULING

The Appeal Board noted that the SPC for Curatoderm did not contain any precautions regarding the use of the product on flexures.

The Appeal Board noted that approximately 20% of psoriatics had flexural psoriasis and so it was inevitable that such patients would have been included in the Van de Kerkhof study which concluded that Curatoderm was well tolerated. In addition the Appeal Board noted that the Chu review supported the general view that Curatoderm was well tolerated even on face and flexures.

The Appeal Board noted that at least 60,000 patients had been treated with Curatoderm. An in-house review of Merck's spontaneously reported adverse reaction data base revealed cases of local skin reactions and so even if all of these had been associated with the flexural application of Curatoderm it would have represented an incidence of less than 1%. The Appeal Board noted that the reporting rate of adverse reactions did not reflect the actual level of side effects associated with a product.

In the Appeal Board's view, when considered overall, the data produced by Merck was sufficient to substantiate the claim "Well tolerated - even in ... flexural psoriasis". The Appeal Board upheld the Panel's ruling of no breach of the Code.

The appeal therefore failed.

Complaint received **25 July 1997**

Case completed **13 November 1997**

CASES AUTH/593/8/97 AND AUTH/594/8/97 *NO BREACH OF THE CODE*

CONSULTANT IN PUBLIC HEALTH MEDICINE/MEDICAL ADVISOR v EISAI AND PFIZER

Aricept advertisement

A consultant in public health medicine/medical advisor complained about a mailing on Aricept sent to pharmacists by Eisai and Pfizer. The complainant alleged that the material was misleading by implying that a woman in a photograph had a mother who had improved sufficiently to restore her memory. The improvement was presumed or inferred to be due to the effect of the product.

The Panel did not accept that the material implied that Aricept restored memory. There was data to support an improvement in cognitive function. The Panel did not consider that the advertisement was misleading with regard to the efficacy of Aricept, it was not claiming that the product was the cure for Alzheimer's disease. No breach of the Code was ruled.

A consultant in public health medicine/medical advisor in a health authority complained about a mailing to pharmacists about Aricept (donepezil) sent by Eisai Limited and Pfizer Limited. The mailing consisted of a "Dear Pharmacist" letter and a four page, A5 leaflet (both ref A010-30044-03-97). The complainant had only enclosed a copy of the leaflet.

Page one of the leaflet in question was headed "Mum has Alzheimer's" beneath which was a sepia photograph of a young woman looking worried. The leaflet opened to reveal page three which had a larger colour photograph of the young woman and her mother, both smiling, with the heading "but she knew I was calling today". On the same page, and beneath the Aricept logo was the claim "A first step in Alzheimer's".

COMPLAINT

The complainant alleged that the Aricept advertisement

was misleading. It was a relatively new medication for the treatment of Alzheimer's disease. Being a new medicine it was licensed on reported research trials that showed a degree of clinical effectiveness over placebo. Only one out of these three research trials had been published and subjected to standard peer review in a medical journal. However, it was a widely held view, or at least widely debated, that the degree of clinical effectiveness was marginal and it was not apparent what this meant in practical terms of clinical outcome or improvement for the patient. Therefore it seemed misleading for the advertisement to imply that the woman in the picture had a mother who had improved sufficiently to restore her memory. The research trials had failed to establish clearly this sort of clinical improvement. The improvement was presumed or inferred to be due to the effect of the product.

The complainant noted that it might well be that in due course the product could demonstrate by further research that it could achieve these clear clinical gains for patients but until this was so the complainant did not think that the advertisement should be allowed to imply such beneficial effects.

Case AUTH/593/8/97

RESPONSE

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

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

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

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

The section in the SPC headed "Pharmacodynamic properties" stated that significant correlation was demonstrated between plasma levels of donepezil hydrochloride, AChE inhibition and change in ADAS cog (Alzheimer's Disease Assessment Scale, cognitive subscale) a sensitive scale which examined memory. The section headed "Pharmacokinetic/dynamic properties - characteristics in patients" stated that in two double blind randomised trials, statistically significant drug placebo differences were present for each of two primary outcome measures (ADAS cog/CIBIC plus) (Clinician's Interview - Based Impression of Change - Plus Version).

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

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

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

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

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

showed that Aricept would provide benefit over and above simple cognitive enhancement in a minority of patients suffering Alzheimer's disease.

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

Case AUTH/594/8/97

RESPONSE

Pfizer submitted that the response from Eisai should be treated as a response on behalf of Pfizer.

Cases AUTH/593/8/97 and AUTH/594/8/97

PANEL RULING

The Panel noted that this complaint had much in common with Cases AUTH/561/5/97 and AUTH/562/5/97 although they were not entirely at one and the new complaint was therefore treated as a fresh matter.

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

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

Complaint received **4 August 1997**

Cases completed **9 October 1997**

CASE AUTH/597/8/97 *NO BREACH OF CODE*

SMITHKLINE BEECHAM v LILLY

Prozac advertisement

SmithKline Beecham submitted a complaint about a journal advertisement for Prozac issued by Eli Lilly. SmithKline Beecham alleged that the heading "True leadership has to be earned" was all encompassing and used a superlative. Further the advertisement implied a link between efficacy and leadership and there was no evidence to support an implied claim that Prozac was the leading SSRI with respect to efficacy.

The Panel considered that the term "True leadership" was not a superlative in the grammatical sense. The Panel considered that neither the layout of the advertisement nor the text made an implied claim that Prozac was the leading SSRI with respect to efficacy as alleged. No breach of the Code was ruled.

SmithKline Beecham Pharmaceuticals UK submitted a complaint about a journal advertisement for Prozac (fluoxetine) (ref PZ 906), issued by Eli Lilly and Company Limited. The advertisement was headed "True leadership has to be earned". Beneath the heading was a photograph of an aerial view of athletes in a road race. One runner was well ahead of the others. Adjacent to the photograph was a subtitle "Associated Anxiety" which was followed by the claim that "Prozac has a proven record of efficacy in depression, with a confirmed indication in depression with or without associated anxiety symptoms. A possible reason why Prozac has earned its status around the world". Beneath the Prozac logo the claim "The World's No. 1 prescribed antidepressant brand" appeared.

COMPLAINT

SmithKline Beecham submitted that the advertisement heading was all-encompassing and that the term 'True leadership' was a superlative. The text focused on the efficacy of fluoxetine in depression with or without associated anxiety symptoms. SmithKline Beecham alleged that such statements appearing under the heading implied a link between efficacy and leadership. SmithKline Beecham submitted that there was no evidence to support an implied claim that fluoxetine was the leading SSRI (selective serotonin re-uptake inhibitor) with respect to efficacy and as such the advertisement was in breach of Clause 7.8 of the Code.

RESPONSE

Lilly submitted that the heading "True leadership has to be earned" was not a claim regarding Prozac nor was it intended to be. It was a simple statement of fact which introduced in a general way the theme of leadership and specifically provided comment on the leader in the road race in the accompanying photograph. Thematic statements were widely used and accepted in

pharmaceutical advertising to set a scene within the context of which a specific and substantiated claim might be placed.

Lilly submitted that the claim in the advertisement was that Prozac was "The World's No. 1 prescribed antidepressant brand". This claim was referenced to data on file. The analogy was therefore made to leadership in world-wide prescriptions of branded antidepressants. This pairing of the thematic statement "True leadership has to be earned" and the specific claim "The World's No. 1 prescribed antidepressant brand" ran throughout the Prozac advertising campaign and would be familiar to most readers.

Lilly submitted that the specific claims regarding the efficacy of Prozac in the treatment of depression with or without associated anxiety symptoms were specific and substantiated claims. There was no implied link between these claims and the heading, "True leadership has to be earned". Lilly pointed out that the efficacy of Prozac was suggested in appropriately tentative terminology as one "possible reason" why Prozac had earned its status as the world's number one prescribed antidepressant brand. No claim was made or implied regarding the efficacy of Prozac relative to other treatments. The reference to Prozac's status around the world at the end of the paragraph made clear the link between the "leadership" statement and "World's No. 1 prescribed antidepressant brand" claim.

Lilly therefore submitted that the advertisement was not in breach of Clause 7.8 of the Code.

PANEL RULING

The Panel noted the supplementary information to Clause 7.8 of the Code that superlatives were those grammatical expressions which denoted the highest quality or degree. The Panel considered that the term 'True leadership' in the advertisement heading was not a superlative in the grammatical sense.

The Panel considered that the general theme of the advertisement was leadership and noted the thematic association between the heading, accompanying photograph, and the reference to "The World's No. 1 prescribed antidepressant brand". The Panel noted that the text referred to both the efficacy of Prozac in depression and the fact that it could be used in the treatment of depression with or without associated anxiety and this was put forward as a possible reason why Prozac had earned its status around the world as the world's No. 1 antidepressant brand. The Panel considered that neither the layout of the advertisement nor the text made an implied claim that Prozac was the leading SSRI with respect to efficacy as alleged.

The Panel ruled no breach of Clause 7.8 of the Code.

Complaint received **5 August 1997**

Case completed **13 October 1997**

CASE AUTH/598/8/97

PHARMACIA & UPJOHN v FRESENIUS

Dipeptiven advertisement

Pharmacia & Upjohn complained about a journal advertisement for Dipeptiven (glutamine) issued by Fresenius.

It was alleged that the claim "The essential way to cut hospital stay" suggested that the use of Dipeptiven was the only way to cut hospital stay. This was unlikely to be the case as other glutamines were available. It was an exaggerated claim where any special merit could not be substantiated. In the Panel's view the immediate impression given by the advertisement was that Dipeptiven specifically was the essential way to cut hospital stay whereas other information in the advertisement referred only to glutamine. Headlines could not be qualified by small print. A breach of the Code was ruled.

The claim "Dipeptiven brings unequalled convenience to providing glutamine" was alleged to be in breach because it could not be substantiated as it suggested that the product had some special merit, quality or property. The Panel noted that Dipeptiven differed from both of its competitors as it was a concentrated form of glutamine intended to be added aseptically to other solutions. The Panel accepted that it would provide flexibility of glutamine dosage and might be a convenient way of providing additional glutamine. The Panel considered however that the claim implied that Dipeptiven was the most convenient way of providing glutamine and this was not necessarily so. It would depend on the practices of particular hospitals. It was a claim for a special merit or property that could not be substantiated and was ruled in breach.

It was alleged that the claim "A new concept in clinical nutrition" could not be substantiated as glutamine administration to hospitalised hypercatabolic and hypermetabolic patients could not be regarded as a new concept in clinical nutrition. In addition, it was alleged that the word "new" was being used for a product which had been on the market for more than twelve months, contrary to the requirements of the Code. The Panel considered that the claim was unacceptable as Dipeptiven had been launched more than twelve months earlier and ruled a breach in that regard. Further, the Panel ruled a breach as it was misleading to describe it as a new concept in clinical nutrition as glutamine had been used as part of clinical nutrition for some time, the studies cited in the advertisement being from 1992 and 1993. It was not considered that the claim was exaggerated and no breach was ruled in that regard.

Pharmacia & Upjohn Limited complained about a journal advertisement for Dipeptiven (glutamine) issued by Fresenius Limited. Fresenius was not a member of the ABPI and nor had it previously agreed to comply with the Code. Following receipt of the complaint, Fresenius agreed to comply with the Code and to accept the jurisdiction of the Authority. The advertisement had appeared in the July/ August 1997 edition of the British Journal of Intensive Care and was entitled "Glutamine for Hypercatabolic and Hypermetabolic Patients".

1 Claim: "The essential way to cut hospital stay"

The advertisement was headed 'Dipeptiven' underneath which, in large type, was the claim, "The essential way to cut hospital stay". Beneath the claim, and to the left of it, were two graphs showing reduced length of hospital stay when using glutamine. The graphs were referenced to studies by Schloerb *et al* (1993) and Ziegler *et al* (1992). Text to the right of the graphs described some of the features of Dipeptiven but one paragraph, referring to reduced hospital stay, only used the generic name, glutamine.

COMPLAINT

Pharmacia & Upjohn stated that the phrase "The essential way to cut hospital stay" would suggest to the reader that the use of Dipeptiven was indeed the only way to cut hospital stay. This was unlikely to be the case as other glutamines were available in the UK. The company considered the phrase to be an exaggerated claim where any special merit of Dipeptiven could not be substantiated. Pharmacia & Upjohn alleged a breach of Clause 7.8.

RESPONSE

Fresenius stated that regardless of the type of glutamine used it had been clearly shown that glutamine reduced hospital stay. This had been clinically proven by Ziegler *et al* and Schloerb *et al*. The graphs in the advertisement illustrated this point and the text stated that hospital stay was reduced with glutamine and not specifically with Dipeptiven *per se*. Fresenius therefore did not consider it to be an exaggerated claim.

PANEL RULING

The Panel noted that "Dipeptiven" and "The essential way to cut hospital stay" both appeared in large type at the top of the advertisement. In the Panel's view the immediate impression given by the advertisement was that the use of Dipeptiven specifically was the essential way to cut hospital stay. The Panel noted that within the advertisement graphs and text referring to reduced hospital stay only referred to glutamine. It was, however, a well established principle of the Code that headlines could not be qualified by small print. The Panel considered that the headline was exaggerated, glutamine had been shown to reduce hospital stay, not Dipeptiven in particular. A breach of Clause 7.8 was ruled.

2 Claim: "Dipeptiven brings unequalled convenience to providing glutamine"

COMPLAINT

Pharmacia & Upjohn stated that this claim could not be substantiated as it would suggest that the product had some special merit, quality or property. The company alleged a breach of Clause 7.8 of the Code.

RESPONSE

Fresenius stated that the claim could be substantiated as Dipeptiven was a concentrate (13.46g glutamine and 8.2g alanine per 100ml) which was available in 50ml or 100ml bottles. It could be easily added to a parenteral nutrition regimen without adding a large volume of fluid. It therefore provided dose flexibility and therefore had a special quality.

Fresenius referred to its two competitor products. Glamin (Pharmacia & Upjohn) contained 20g glutamine per litre and essential and non-essential amino acids and was available in volumes of 500ml or 1 litre. L-glutamine (Oxford Nutrition) contained 25g L-glutamine per litre and was available in frozen 1 litre bags.

Fresenius noted that the volumes of fluid of its competitor products were much greater than in Dipeptiven. In addition L-glutamine had to be defrosted before it could be used. Also, Pharmacia & Upjohn added all the other amino acids to Glamin which meant that there was little flexibility in its use. With Dipeptiven, the user had the flexibility of adding the amino acid of choice.

PANEL RULING

The Panel noted that Glamin was a complete solution of free amino acids and dipeptides for intravenous nutrition. Glamin contained 18 essential and non-essential amino acids to be used as part of a parenteral nutrition regimen. To achieve a complete parenteral nutrition regimen, Glamin was administered in combination with carbohydrates and/or fat as well as electrolytes, trace elements and vitamins (ref Glamin data sheet; ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1996-97).

Dipeptiven contained only glutamine and alanine and was indicated as part of an intravenous parenteral nutrition regimen as a supplement to amino acid solutions or an amino acid containing infusion regimen in patients whose condition required additional glutamine. Dipeptiven had to be added aseptically to other solutions, the Summary of Product Characteristics stated a dilution of 1 part of Dipeptiven with at least 5 parts of carrier solution, eg amino acid solution. It was not intended for direct administration. In the Panel's view Dipeptiven would, for the most part, be added to commercially available fixed combinations of amino acids. This admixture would then in turn form part of a complete parenteral nutrition regimen.

The Panel accepted that, unlike L-glutamine from Oxford Nutrition, Dipeptiven did not need defrosting and that compared to both of its competitors it was a concentrated form of glutamine. The Panel accepted that Dipeptiven would provide flexibility of glutamine dosage and might be a convenient way of providing additional glutamine. Much would depend on the practices of particular hospitals. The Panel considered, however, that the claim in question "Dipeptiven brings unequalled convenience to providing glutamine" implied that Dipeptiven was the most convenient way of providing glutamine and this was not necessarily so. The Panel considered that the claim was for a special merit quality or property that could not be substantiated. The Panel therefore ruled a breach of Clause 7.8 of the Code.

3 Claim: "A new concept in clinical nutrition"

This claim was used as a strapline immediately beneath the product name at the bottom of the advertisement.

COMPLAINT

Pharmacia & Upjohn stated that the strapline could not be substantiated as glutamine administration to hospitalised hypercatabolic and hypermetabolic patients could not be regarded as a new concept in clinical nutrition.

The company regarded the statement as exaggerated and not capable of substantiation and alleged a breach of Clauses 7.8 and 7.2. In addition Pharmacia & Upjohn alleged that the use of the word "new" for a product which had been on the market for more than twelve months was in breach of Clause 7.9.

RESPONSE

Fresenius stated that the provision of glutamine in clinical nutrition was a new concept and this was clearly evident from the amount of clinical research in this area at present. Historically, clinicians considered glutamine to be a non-essential amino acid. However, it was now considered to be "conditionally essential". This statement was therefore wholly substantiated.

Fresenius confirmed that Dipeptiven had been launched in April 1996.

PANEL RULING

The Panel noted the requirements of Clause 7.9 of the Code which stated that "The word 'new' must not be used to describe any product or presentation which has been generally available ... for more than twelve months in the UK".

The Panel considered that the claim "Dipeptiven a new concept in clinical nutrition" was unacceptable as Dipeptiven had been launched more than 12 months ago. A breach of Clause 7.9 was ruled. Further, the Panel considered that it was misleading to describe Dipeptiven as a new concept in clinical nutrition as glutamine had been used as part of clinical nutrition for some time. In this regard the Panel noted that the benefits of glutamine described in the advertisement were referenced to studies dated 1992 and 1993. The Panel therefore ruled a breach of Clause 7.2 of the Code. The Panel did not consider that the claim was exaggerated and no breach of Clause 7.8 was ruled.

Complaint received **6 August 1997**

Case completed **26 November 1997**

CASE AUTH/599/8/97

ANON v MERCK SHARP & DOHME

Conduct of representatives

Two invitation cards were copied and sent anonymously to the Authority. One was headed "Come and taste the difference...MSD" and invited people to a "Walk in Lunch" at a restaurant. It bore the first names only of four Merck Sharp & Dohme representatives. The Panel noted that although no reference was made to it on the invitation, there was in fact a presentation by a local general practitioner on osteoporosis audit. Lunch was available over a two hour period and the presentation began when the expected number had arrived. That was why it was called a "Walk in Lunch". The Panel considered that the invitation gave the impression that the meeting was for social purposes only and that the educational content was not sufficient to justify the associated hospitality. It was ruled that there had been breaches of the Code in that the representatives had failed to maintain a high standard of ethical conduct and comply with relevant provisions of the Code, the hospitality was unacceptable. A breach of Clause 2 was ruled as the impression given by the invitation brought discredit upon the industry.

Merck Sharp & Dohme accepted that its representatives had failed to maintain high standards but appealed the rulings relating to the provision of hospitality and the breach of Clause 2. The Appeal Board considered that the impression given by the invitation card was that the primary purpose of the meeting was to have a meal and that it was a social event. The scientific content was not sufficient to justify the hospitality. The Appeal Board upheld the Panel's rulings.

The second invitation was headed "Come and help us celebrate the 50th anniversary of India's independence". Recipients were invited to join four Merck Sharp & Dohme representatives, whose first names only were given, for a cultural evening followed by dinner at a restaurant.

The Panel noted that the cultural evening consisted of a play written by the daughter of a local general practitioner who had bought all of the tickets for the event. Those having dinner afterwards paid for themselves. The Merck Sharp & Dohme representatives had helped to advertise the event but had not attended it. Merck Sharp & Dohme was not involved in the event and viewed it as a personal matter between its representatives and the GP who happened to be a personal friend of two of them. The Panel considered that the wording of the cards was inadequate in describing the arrangements for the evening. The invitation said that the play was followed by dinner and there was no indication that diners would have to pay. The impression was that Merck Sharp & Dohme was involved and, in the Panel's view, this was unacceptable. It was a social event with no educational content and was ruled in breach. The provision of the cards and their use in the course of promotion by the representatives meant that they had failed to maintain a high standard of ethical conduct and a breach was ruled. The Panel considered that the circumstances brought discredit upon the industry and ruled a breach of Clause 2.

Merck Sharp & Dohme again accepted that its representatives had failed to maintain a high standard but appealed the rulings relating to the provision of hospitality and the breach of Clause 2. The Appeal Board considered that the impression was that the representatives were involved in a social event without educational content which was unacceptable and upheld the Panel's ruling in that regard. The Appeal Board did not consider that the industry had been brought into disrepute and overturned the Panel's ruling of a breach of Clause 2 in that respect. The card did not mention the company and no hospitality had been provided.

COMPLAINT

An anonymous complaint was received about two events. The first was a restaurant lunch and the second was a cultural evening to celebrate the 50th anniversary of India's independence. There was no letter of complaint but the complainant provided a photocopied sheet with details about a representative from Merck Sharp & Dohme Limited and two invitation cards inviting recipients to the events in question.

Lunch at a restaurant

The invitation card was entitled "COME AND TASTE THE DIFFERENCE...MSD" It invited people to a "Walk in Lunch" at a restaurant and asked people to confirm their attendance by telephone with the four representatives, whose first names only were given. One telephone number was given. Beneath the text was a map showing the location of the restaurant.

RESPONSE

Merck Sharp & Dohme stated that the event was a medical meeting organised by the four representatives mentioned on the invitation card. The speaker at the meeting was a local general practitioner and the subject of the discussion was his experiences performing an osteoporosis audit in general practice. The restaurant was hired specifically for the occasion by the representatives and was not open to the public.

The meeting followed a slightly different format from a traditional representative meeting. Lunch was provided from 12.30pm and the restaurant closed at 2.30pm. There was no set time for the speaker to begin his presentation. It was agreed that he would begin when the expected number of attendees arrived. This arrangement was in recognition of the fact that doctors' morning surgeries finished at various times, typically between 12.30pm and 1.00pm. Merck Sharp & Dohme submitted that by making lunch available from 12.30pm and not specifying the start time for the presentation they were maintaining flexibility to ensure that the maximum number of GPs possible should hear the presentation. This was the meaning behind the phrase "Walk in Lunch".

Merck Sharp & Dohme said that this was the first time that the representatives had held a joint meeting of this type. One of the representatives named on the invitation card had previously held a meeting at the restaurant and a number of GPs had got lost on the way. The

representatives were therefore asked if they could produce a small map to ensure that the GPs should all arrive in good time. Merck Sharp & Dohme pointed out that the card sent to the Authority was one of these maps.

Merck Sharp & Dohme submitted that the level of hospitality was appropriate. A standard Indian restaurant buffet was offered to attendees at a cost of £12 per head. Merck Sharp & Dohme submitted that the meeting was a perfectly acceptable medical educational meeting and was therefore not in breach of Clauses 19 or 2 of the Code. Merck Sharp & Dohme did concede however that the phrases "Come and Taste the Difference..." and "Walk in Lunch" might well have created an incorrectly poor impression of the meeting and accepted that the Panel might consider that a breach of Clause 15.2 had occurred. Merck Sharp & Dohme stated that appropriate disciplinary measures had been taken against the representatives.

Finally, Merck Sharp & Dohme pointed out that one of the representatives mentioned on the invitation card did not work for Merck Sharp & Dohme Limited but for Innovex, a rental sales force working on behalf of Merck Sharp & Dohme. Merck Sharp & Dohme accepted that the actions of the sales representative were the actions of Merck Sharp & Dohme for the purposes of this complaint and had passed its findings to Innovex for it to take appropriate action.

PANEL RULING

The Panel noted Clause 19 and its supplementary information which stated that meetings must have a clear educational content. Companies were permitted to provide appropriate hospitality to health professionals in association with such meetings. Hospitality had to be secondary to the purpose of the meeting, the level must be appropriate and not out of proportion to the occasion and the costs must not exceed that level which the recipients would normally adopt when paying for themselves. The Panel examined the text and layout of the invitation. There was no general indication of any medical or educational content to the lunchtime meeting and no specific reference made to the presentation to be given. The Panel considered that the invitation gave the impression that the lunch was for social purposes only.

The Panel did not accept that the invitation card was merely a map to ensure that the invited GPs arrived at the restaurant in good time. The invitation card was the only document which was given to GPs. The Panel noted from the company's submission that there was to have been some educational content to the meeting but the arrangements appeared vague and there was no programme etc. In the Panel's view the impression from the invitation was that the educational content was not sufficient to justify the associated hospitality. The Panel therefore ruled a breach of Clause 19.1 of the Code.

The Panel also ruled a breach of Clause 15.2 of the Code as the representatives had failed to maintain a high standard of ethical conduct and comply with all relevant requirements of the Code.

The Panel considered that the impression given by the invitation, that the lunch was a social event, brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 of the Code was also ruled.

Cultural Evening

The second invitation card was headed "COME HELP US CELEBRATE THE 50TH ANNIVERSARY OF INDIA'S INDEPENDENCE". The recipients were invited to join four representatives, whose first names only were given, for a cultural evening followed by dinner at a restaurant. The cultural evening consisted of a play and took place at a local theatre. Recipients of the card were asked to confirm their attendance by telephoning one of two of the representatives mentioned on the invitation card and whose telephone numbers were given.

RESPONSE

Merck Sharp & Dohme stated that, as explained on the invitation card, the play was adapted by the daughter of a local GP. Two of the representatives mentioned on the invitation card were personal friends of the GP and were asked by the GP to help advertise the play. The representatives did this by supplying posters to local banks, building societies and the like and also by the production of the cards, one of which was sent to the Authority. The cards were provided to doctors upon request or would be offered to GPs by the four representatives at the end of a promotional call.

Merck Sharp & Dohme confirmed that neither the representatives nor Merck Sharp & Dohme defrayed any of the costs associated with either the play or the dinner afterwards. All of the tickets for the event were purchased by the GP and the attendees each paid for their dinner afterwards. Merck Sharp & Dohme pointed out that none of the four representatives attended either the play or the dinner.

Merck Sharp & Dohme viewed this as an entirely personal manner between the representatives and one of their customers who happened to be a personal friend of two of them. Merck Sharp & Dohme pointed out that the company was in no way involved with the arrangements. It had not met any of the costs associated with the event and the evening was not associated with product promotion. Accordingly, submitted Merck Sharp & Dohme, there was no breach of the Code.

PANEL RULING

The Panel noted the supplementary information to Clause 19 of the Code that meetings organised for health professionals etc which were wholly or mainly of a social or sporting nature were unacceptable.

The Panel noted the submission from Merck Sharp & Dohme that two of the representatives were personal friends of the GP and were asked to help advertise the play. The Panel did not accept that the event was an entirely personal matter as, if that were so, it was not necessary to put the representatives' names on the invitation. The Panel noted that the invitation stated that the recipients were invited to join the named representatives for a cultural evening followed by dinner at a restaurant. The impression was that the event was organised and paid for by the representatives. The Panel

noted that the representatives did not actually attend the event. The invitation did not make clear the arrangements that attendees were expected to pay for their meal and that the GP concerned had paid for the theatre tickets. The Panel noted that although the cards did not carry the name of the company they did carry the first names of the representatives and were offered to GPs at the end of a promotional call and so would be associated with the company.

The Panel considered that it could be difficult when representatives were personal friends of doctors they called upon. Clear distinctions should be made between business and personal arrangements. The Panel considered that the wording of the cards was inadequate in describing the arrangements for the evening as detailed by Merck Sharp & Dohme in its response. The impression was that the company was involved in the event and in the Panel's view this was unacceptable. It was purely a social event. There was no educational content. The Panel therefore ruled a breach of Clause 19.1 of the Code.

The Panel considered that the provision of the cards and their use during the course of promotion meant that the representatives had failed to maintain a high standard of ethical conduct. The Panel therefore ruled a breach of Clause 15.2 of the Code.

The Panel considered that the circumstances brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

APPEAL BY MERCK SHARP & DOHME

Merck Sharp & Dohme said that it accepted the findings of breaches of Clause 15.2 but wished to appeal against the findings of breaches of Clauses 2 and 19.1 in respect of both events.

Merck Sharp & Dohme made two preliminary observations arising from the complaint.

1 This was an anonymous complaint. Merck Sharp & Dohme accepted entirely the need to provide a mechanism under the Code to allow for complaints to be raised against companies where the complainant did not wish to identify himself or herself. Nevertheless, such complaints placed the respondent company in an extremely difficult position. This was compounded in a case such as this one where the complainant did not even set out their version of events. The respondent company could not know what charges, in detail, they were expected to meet. The best they could, therefore, do was to investigate the case fully and set out their version of events for the Panel's consideration.

In fairness to the respondent, however, Merck Sharp & Dohme believed it was incumbent upon the Panel to accept this version of events except where there was clear evidence to the contrary. Merck Sharp & Dohme did not believe it was reasonable in these circumstances for the Panel to act on mere inferences drawn from the material before them, where this inference was directly at odds with the facts set out by the respondent.

2 Merck Sharp & Dohme drew the attention of the Appeal Board to the wording of Clause 19.1 which referred to "appropriate hospitality", noting that it must be "secondary to the purpose of the meeting" and also that it must be "not out of proportion to the occasion". In addition, it also set out that "the costs involved must not exceed that level which the recipients would normally adopt when paying for themselves". The rather helpful supplementary information to the clause used similar terms. Merck Sharp & Dohme submitted therefore, that a breach of Clause 19.1 should only be ruled where it was established that the level of hospitality actually offered by the company was in some way inappropriate. It should not be ruled merely where the material surrounding the offer of hospitality might give that impression. Merck Sharp & Dohme believed that, in the latter case, the more appropriate course for the Panel was to rule a breach of Clause 15.2, as occurred in this case.

Merck Sharp & Dohme noted that the supplementary information to Clause 19.1 stated "The impression that is created by the arrangements for any meeting must always be kept in mind". While this provided guidance on the approach which the Panel would take in considering the actual level of hospitality offered, Merck Sharp & Dohme did not believe it was sufficient to justify a finding of breach of Clause 19.1 where both the level of hospitality offered and the educational content of the meeting were entirely appropriate.

Lunch at a restaurant

This meeting was organised by four Merck Sharp & Dohme representatives; a local general practitioner was asked to address a group of GPs about an osteoporosis audit which he had recently undertaken in his practice. The aim of the meeting was to encourage other doctors to undertake similar audits. The meeting was to be held at a restaurant which had been booked out by the representatives and accordingly was not open to the public on that day. Knowing that morning surgeries tended to finish at different times, the meeting was arranged such that lunch would be available for the attendees from 12.30pm, although the speaker would not begin his presentation until most of those who had been invited had arrived. As was common for lunchtime meetings (which tended to be smaller and less formal) no written invitations were issued, and the invitees were notified of these arrangements personally by the representatives in question.

The company's representatives confirmed that scientific and educational lunchtime meetings were held approximately once every fortnight. To require written invitations for such meetings and formal documents would create too much paperwork for the sales representatives.

The restaurant was relatively new and hard to find; the representatives were, therefore, asked on numerous occasions for written directions as a number of GPs had missed previous meetings at the restaurant, being unable to find it. The restaurant was situated on a very long road which made it difficult to find and had an awning outside which obscured the name. In response to these requests, the representatives produced the map which formed part of the complaint.

The company's representatives confirmed that the catch-phrase of the restaurant was "Indian food with a difference". This was the origin of the phrase, "Come and taste the difference...", used on the card.

The presentation began at about 1.15pm and continued for some twenty to twenty-five minutes, including questions. There were about eighteen GPs at the meeting when the speaker began his presentation and others arrived during the course of it. By the end of his presentation there were some thirty doctors present. The speaker and the representatives then circulated among the attendees, discussing clinical audit and how Merck Sharp & Dohme could assist local practices in setting them up. The last GP left the meeting at about 2.30pm.

A letter from the speaker was provided for the Appeal Board. The company's representatives confirmed that the letter had been produced in connection with disciplinary proceedings taken against the representatives in question. The letter stated that:

"This is to confirm that I attended a medical meeting at the ..... Restaurant on the 18th July 1997 during lunchtime. I had informal discussions with my colleagues regarding osteoporosis, auditing and the treatment, mainly Fosamax and other calcium supplementation etc. This was a friendly meeting which went on very well.

In the many years that I have known ..... and ..... and also ..... and ..... for the last few months they have always exhibited the highest professionalism and integrity".

Merck Sharp & Dohme accepted the finding of a breach of Clause 15.2 of the Code. The words "Come and taste the difference ... MSD" were wholly inappropriate and gave a misleading impression of the meeting. The expression "walk in lunch" was intended to refer to the fact that there was no formal time set for the presentation to begin and that the talk would start when most of the audience had arrived.

Merck Sharp & Dohme did not, however, believe that the meeting itself was in any way inappropriate or a breach of the Code. There was a clear scientific and educational content to the meeting and the level of hospitality offered was entirely reasonable. The bill from the restaurant was provided.

As set out above, Merck Sharp & Dohme did not believe the Panel should have concluded that the arrangements for the meeting were anything other than satisfactory. Merck Sharp & Dohme had provided its version of events. These were entirely consistent with the details set out on the map submitted to the Authority. In the absence of any evidence, Merck Sharp & Dohme did not believe it was open to the Panel to suggest that the meeting itself was in any way a breach of the Code. In the circumstances, Merck Sharp & Dohme also did not believe that the Panel was entitled to rule a breach of Clause 19.1. It seemed clear to Merck Sharp & Dohme that Clause 19 was intended to prevent inappropriate levels of hospitality at meetings organised by, and paid for, by companies. It was not, however, intended to deal specifically with inappropriately worded invitations to otherwise perfectly acceptable meetings. Merck Sharp & Dohme believed that this was better dealt with under Clause 15.2.

In the light of the above, Merck Sharp & Dohme believed that the finding of a breach of Clause 2 was both unwarranted and unfair. While Merck Sharp & Dohme accepted that its representatives were guilty of poor judgement in the phrasing of the invitation to the meeting, it did not believe that this alone justified a finding of a breach of Clause 2. Such a finding might have been appropriate if the level of hospitality offered had been as lavish as the Panel implied. However, this was not so and Merck Sharp & Dohme, therefore, believed it to be unreasonable.

Cultural Evening

The play was written by the daughter of a local GP; the GP was also a close personal friend of two of the representatives in question. The GP had underwritten the entire cost of the evening (some £4,000) and proposed to sell some tickets, while distributing others free to GP colleagues and selected guests. In addition, the GP proposed to organise dinner afterwards for some of the guests, the cost of which would be met by the diners themselves.

The GP asked Merck Sharp & Dohme's representatives whether they would be willing to help in promoting the event; they agreed. They distributed a number of posters (provided by the GP) to local restaurants and supermarkets. In addition, they produced a number of card invitations, one of which formed the second part of the complaint. They also negotiated a discounted rate for those who wished to dine at the restaurant afterwards.

The cards were distributed to local GPs by the representatives. This usually took place at the end of a promotional call; however, some were also distributed whenever the representative happened to meet a local doctor. When a prospective attendee rang either of the representatives named on the invitation, the representative would make a note of the name; they then presented a list of those intending to attend to the GP before the event. Doctors simply picked up tickets from the GP on the night of the performance. The financial arrangements for the evening were made clear to each doctor when the invitation was given to them. The tickets for the event were free (courtesy of the GP) but they would be expected to pay for dinner at the restaurant afterwards.

This was the sum total of Merck Sharp & Dohme's involvement; the representatives did not even attend the event itself.

The company confirmed that this complaint had been submitted prior to the date of the cultural evening and hence the company had advised the representatives in question not to attend the event.

A letter of clarification from the GP was provided.

At the time of the original complaint, Merck Sharp & Dohme denied that any breach of the Code had occurred. Having read the ruling of the Panel, however, it accepted that the invitation could have been better worded in order to make clearer the financial arrangements for the event. Accordingly, it did not appeal against the finding of a breach of Clause 15.2 of the Code. Again, and for the reasons set out above, it denied that a finding of a breach of Clause 19.1 was appropriate in this case. Merck Sharp & Dohme's submission was that, while the hospitality offered on the evening was in any event reasonable, this was irrelevant as neither Merck Sharp & Dohme nor its representatives played any part in defraying its cost. The hospitality was not, therefore, "provided" by Merck Sharp

& Dohme as required by Clause 19.1 of the Code. In the absence of evidence supporting its view, it did not believe it open to the Panel to have implied to the contrary. Merck Sharp & Dohme believed that this was also more appropriately dealt with by a finding of breach of Clause 15.2.

As above and while Merck Sharp & Dohme accepted that the representatives were guilty of an error of judgement, it believed that this fell far short of conduct required to justify a finding of breach of Clause 2 of the Code.

APPEAL BOARD RULING

Lunch at a restaurant

The Appeal Board noted that the invitation card referred to "MSD". It examined the letter from the speaker and considered that it did not give the impression that the meeting had had a substantive scientific content. The Appeal Board considered that the impression given by the invitation card was that the primary purpose of the meeting was to have a meal. The Appeal Board considered that the scientific content of the meeting was not sufficient to justify the hospitality provided. The Appeal Board upheld the Panel's ruling of a breach of Clause 19.1 of the Code.

The Appeal Board considered that the impression given by the invitation card, that the lunch was a social event, brought discredit upon and reduced confidence in the pharmaceutical industry. The Appeal Board upheld the Panel's ruling of a breach of Clause 2 of the Code.

The appeal therefore failed.

The Appeal Board was extremely concerned about the way Merck Sharp & Dohme allowed its representatives to organise lunchtime meetings without the need for written invitations or any formal documents. In the Appeal Board's view the company's procedures were inadequate to ensure that lunchtime meetings complied with the Code. The Appeal Board recommended that Merck Sharp & Dohme be advised to review its procedures.

Cultural Evening

The Appeal Board noted that the cards had been handed out by the representatives following GP calls. The cards did not mention the company by name. The first names of the representatives appeared on the cards.

The Appeal Board considered that the wording of the cards was inadequate in describing the arrangements for the evening as detailed by Merck Sharp & Dohme. The impression was that the representatives were involved in a social event without any educational content and in the Appeal Board's view this was unacceptable. The Appeal Board upheld the Panel's ruling of a breach of Clause 19.1 of the Code.

The Appeal Board noted that the cards did not mention the company. It was intended that diners paid for their own meal and doctors had been told verbally that they would have to pay for their meal. No hospitality had been provided.

The Appeal Board considered that the circumstances did not amount to a breach of Clause 2 of the Code. The Appeal Board therefore ruled no breach of that clause.

The appeal was accordingly partly successful.

Complaint received **6 August 1997**

Case completed **3 December 1997**

CASE AUTH/600/8/97

HOSPITAL PHARMACIST v ASTRA

Inducement to purchase

A hospital principal pharmacist complained that Astra had been negotiating with his Trust in relation to the provision of a consultant management development programme but had withdrawn from the negotiation process when the Trust's formulary was amended to change from omeprazole (Astra's product Losec) to lansoprazole for routine prescribing in a number of indications. The complainant alleged that Astra had linked collaboration on management training to the use of omeprazole in breach of the Code.

The Panel considered that the impression given by a letter to the Trust from Astra was that the provision of support for the development programme was dependent on the formulary remaining unamended with regard to the use of omeprazole. The letter linked its use directly to the provision of training, which was an inducement to purchase contrary to the Code, and a breach was accordingly ruled.

COMPLAINT

A hospital principal pharmacist submitted a complaint about the activities of Astra Pharmaceuticals Ltd.

The complainant stated that in February 1997 his Trust's drug and therapeutics committee amended its policy on proton pump inhibitors. A copy of a memorandum, dated 2 April 1997 and sent from the pharmacy department to all medical, nursing and pharmacy staff, was provided. The memorandum explained that, as from 7 April 1997, lansoprazole (Zoton) would be used in place of omeprazole (Astra's product Losec) for the short and long term management of gastro oesophageal reflux disease, healing and maintenance therapy for patients with duodenal ulcer and healing of benign gastric ulcer. Omeprazole would continue to be used for *H pylori* eradication, Zollinger-Ellison syndrome and in paediatrics.

On 7 April representatives of Astra held a meeting with the Trust chief executive and his colleagues from the personnel department to discuss collaboration between the Trust and Astra in the provision of management training for the Trust's consultants. Members of the drug and therapeutics committee did not know of these discussions and the chief executive and representatives of the personnel department did not know of the decision of the drug and therapeutics committee.

The complainant stated that subsequent to that meeting the chief executive received a letter dated 21 April 1997 from Astra's regional contracts manager.

The letter referred to the preliminary discussions held on 7 April and stated that the regional contracts manager was initially encouraged by the nature and content of the discussion and that there "... would certainly be areas for potential collaboration between Astra and ... NHS Trust". The letter stated that additional information had been received relating to the consultant management development programme and internal discussions regarding the various projects discussed had been initiated. The final paragraph of the letter stated that "However, it has come to my attention, that a memorandum, Ref. ..., was issued on the 2nd April by the Pharmacy Department to all medical, nursing and pharmacy staff. I feel that this memorandum needs to be retracted if discussions are to progress between Astra and ... NHS Trust."

The complainant stated that the chief executive replied to Astra stating that there was no intention of withdrawing the memorandum. The complainant had had discussions with the chief executive and the assistant chief executive. The complainant alleged that the conduct of Astra in linking collaboration on consultant management training between Astra and the Trust with the use of omeprazole was in breach of Clause 18.1 of the Code.

RESPONSE

Astra stated that it was in preliminary negotiations with the NHS Trust for a new contract for the purchase of the company's products. During this process a meeting was held between the Trust, which was represented by the chief executive, the director of personnel, the medical staffing manager and the medical director, and Astra, which was represented by the regional contracts manager and a company representative. At this meeting the principle was discussed of offering an added value package deal as part of the purchasing contract which could be implemented after the revision of Executive Letter EL(94) 94. Astra pointed out that this was an exploratory discussion intended to identify how Astra could meet the needs of the Trust most effectively. The representatives of Astra did not promote specific products or their benefits at the meeting. However, the offer of services to the Trust, instead of discounting the company's products, was discussed. It was agreed in principle that the Trust might have been prepared to contract with Astra for the provision of agreed levels (based upon current usage) of Astra's product range, including Losec, if Astra was prepared to consider supporting one of a number of projects of importance to the Trust. The Trust suggested three alternative projects all of which required a degree of funding. One such project was the consultant management development programme, details of which were provided to the Panel.

Astra submitted that Clause 18.1 did not prevent the offer of package deals whereby the purchaser of particular medicines received with them other associated benefits provided that the transaction as a whole was fair and reasonable. The benefit of the consultant management development programme offered was related to the practice of medicine. The programme was for new consultants throughout the region and was of no personal benefit to any of the members of the Trust attending the meeting. Astra submitted that the package deal offered in the negotiations was fair and reasonable.

Astra stated that part of the negotiations was based upon a certain level of purchase of Astra products. Soon after the meeting the Trust decided to remove Losec from the formulary for the majority of patients requiring treatment with a proton pump inhibitor. Astra submitted that this decision was clearly going to affect the level of purchase of its products. In the absence of the same level of purchase, Astra considered that there was no reason to progress the preliminary discussions.

Astra pointed out that at no time was it trying to influence prescribing. It did not accept that inclusion on the formulary was the same as prescribing. The formulary controlled which products were stocked and in what quantity in the pharmacy. This was not the same as what was prescribed which was decided by the doctors. Therefore any influence on the formulary was not the same as influencing prescribing.

Astra submitted that at all times it had maintained high standards, recognising the special nature of medicines and the professional standing of the audience to which they were directed and with the provision of training for consultants the company wished to increase confidence in the pharmaceutical industry.

Astra submitted that the decision not to progress these preliminary discussions was part of negotiation of a purchasing contract. The provision of consultant training was not intended to influence prescribing in any way.

PANEL RULING

The Panel noted that the offer of discounts on the supply of medicines was a well established and recognised practice within the pharmaceutical industry which fell outside the scope of the Code, although the offer of other pecuniary advantages as inducements to prescribe, supply, administer or buy any medicine were prohibited under Clause 18.1. The Panel noted the supplementary information to Clause 18.1 of the Code headed 'Package Deals'. This stated that package deals might be offered "... whereby the purchaser of particular medicines receives with them other associated benefits, such as apparatus for administration, provided that the transaction as a whole is fair and reasonable." The supplementary information to Clause 18.1 which concerned the provision of medical and educational goods and services was not applicable in this case as the offer of the management development programme was clearly linked to the promotion of Astra's products.

The Panel did not accept the submission from Astra that the arrangements constituted a fair and reasonable

package deal. In the Panel's view, in order for arrangements to be seen as a package deal, the associated benefits had to be relevant to the medicine or medicines purchased. This was the import of the word "associated". For example, the purchase of an anaesthetic might be linked to the provision of a machine to administer that anaesthetic. A management development programme was not relevant to Astra's range of medicines.

The Panel noted that the Trust's drug and therapeutics committee had decided to amend the omeprazole entry in the formulary. From 7 April 1997, lansoprazole was to be routinely prescribed in place of omeprazole for patients commencing treatment for the short and long term management of gastro oesophageal reflux disease (GORD), healing and maintenance therapy for patients with duodenal ulcer and healing of benign ulcer.

The Panel noted that the level of funding for the consultant management development programme was related to a contract with Astra for the provision of agreed levels (based on current usage) of Astra's product range. The Panel noted that the level of funding was intended to be in lieu of a discount. The change in the formulary with regard to omeprazole would mean that the Trust would use less omeprazole and hence the current usage of Astra's product range would fall. Although Astra had made a distinction in its response between influencing the content of a formulary and influencing prescribing, it was evident from the letter from Astra to the chief executive of the Trust of 21 April 1997 that it considered that usage of omeprazole would fall. The Panel considered that the impression given by the letter was that the provision of financial support to the consultant management development programme was dependent upon the formulary remaining unamended with regard to the use of omeprazole.

The Panel noted that given the amendment to the formulary which would have an effect on the usage of Losec, Astra had decided to withdraw completely from the negotiation process. The letter linked the use of Losec directly to the provision of medical training which was an inducement to purchase contrary to the provisions of Clause 18 of the Code. The Panel therefore ruled a breach of Clause 18.1 of the Code.

The Panel noted that the Code was difficult to apply to package deals and the like and that a working party had been established to review the position and make recommendations on the matter.

Complaint received **7 August 1997**

Case completed **4 November 1997**

CASE AUTH/601/8/97 *NO BREACH OF THE CODE*

GENERAL PRACTITIONER v ROSEMONT

Promotion at a residential home

A general practitioner complained about the conduct of a representative from Rosemont who visited a residential home and informed staff of the availability of oral liquid medicines produced by Rosemont.

The Panel considered that health professionals at residential homes or nursing homes would be interested in the availability of medicines in oral liquid form. The Panel considered it reasonable for representatives to visit such homes to promote such products and ruled no breach of the Code.

COMPLAINT

A general practitioner complained about the conduct of a representative from Rosemont Pharmaceuticals Ltd. The complainant alleged that the representative in question had visited a residential home in the vicinity of the complainant's surgery and informed staff at the home of the availability of oral liquid medicines produced by Rosemont. The complainant was concerned that this activity might be in breach of the regulations governing the activities of medical representatives.

RESPONSE

Rosemont confirmed that its sales representative visited the residential home in the belief that it was a nursing home as stated in the company's records. The representative presented the company's products to a member of staff who was very informed on the medication of the patients in terms of which products they were given and how they were administered, implying that this person was qualified. Rosemont conceded that the correct medical qualifications of this person were not known as they were not recorded. The representative could not remember the name of the person concerned. When leaving the residential home the representative left a brochure, a product list and a yellow flyer for further reference. Copies of these items were provided.

Upon receipt of this complaint Rosemont tried to verify the qualification of the person the representative had spoken to and the matron stated that the representative must have spoken to the manager, a qualified nurse, who had left two months ago.

Rosemont submitted that it was not in breach of the Code because its sales representative, herself being a qualified nurse, acted in good faith, presenting the company's products to a member of staff whom she regarded as qualified, although further details could not be obtained. Rosemont confirmed that to prevent any further misunderstandings it would again instruct representatives to verify the professional qualifications of the staff to whom they present the company's products.

PANEL RULING

The Panel considered that health professionals at residential homes or nursing homes would look after a high proportion of elderly residents. Such residents invariably experienced difficulty swallowing medicine in solid dosage forms. The Panel considered that health professionals at residential homes would be interested in the availability of medicines in oral liquid form. The Panel considered it reasonable for representatives to visit such homes to promote such products and ruled no breach of the Code.

During its consideration of this case the Panel was concerned that the sales representative had failed to confirm the identity and status of the person to whom she sought to promote the company's products. The Panel considered that before representatives promoted their products to anyone they should ensure that they knew who they were talking to and knew that they were either health professionals or appropriate administrative staff. The Panel requested that its views be made known to Rosemont.

Complaint received **7 August 1997**

Case completed **20 October 1997**

CASE AUTH/602/8/97 *NO BREACH OF THE CODE*

PROCTER & GAMBLE v DUMEX

Advertisement for Elyzol Dental Gel

Procter & Gamble complained about a journal advertisement for Elyzol Dental Gel issued by Dumex. It was alleged that a claim that two simple steps gave a significant clinical result lasting up to 18 months was not in accordance with the marketing authorization and its inclusion consequently misled general dental practitioners. The licensed indication for Elyzol was "the treatment of chronic periodontal disease as an adjunct to conventional therapy". In the field of periodontal treatment, conventional therapy was universally accepted as scaling and root planing. The claim at issue was referenced to a study in which Elyzol was not used in an adjunctive manner following scaling and root planing in accordance with the marketing authorization. Procter & Gamble submitted that the study demonstrated that both scaling and root planing alone, and the use of Elyzol alone, gave significant clinical results.

The Panel did not agree with Procter & Gamble's view that the referenced study demonstrated that Elyzol alone, and the use of scaling and root planing alone, gave significant clinical results. While the purpose of the study was to compare those two treatments, all patients in the study had undergone previous subgingival scaling and all were involved in ongoing periodontal treatment. In the Panel's view, the introduction of Elyzol to those patients constituted adjunctive therapy. The Panel considered that the product was being used within its licensed indication. The claim was not misleading. No breach of the Code was ruled.

Procter & Gamble Healthcare Products Europe complained about a journal advertisement for Elyzol Dental Gel issued by Dumex Limited. Dumex was not a member of the ABPI but had nevertheless agreed to comply with the Code.

Elyzol Dental Gel was indicated in the treatment of chronic periodontal disease as an adjunct to conventional therapy. The gel was to be administered into the periodontal pocket twice with a one week interval.

COMPLAINT

Procter & Gamble alleged that the claim "TWO SIMPLE STEPS give a SIGNIFICANT CLINICAL RESULT lasting up to 18 MONTHS" referenced to a paper by Stelzel *et al* (1994) was in breach of Clauses 3.2 and 7.2 of the Code. Procter & Gamble alleged that the claim was not in accordance with the marketing authorization and its inclusion in promotional material consequently misled general dental practitioners.

Procter & Gamble noted that the claim was supported by reference to Stelzel M *et al*, presented at the American Association of Periodontology 80th annual meeting, San Francisco, September 1994. Procter & Gamble submitted that this study demonstrated that both scaling and root planing alone and use of Elyzol Dental Gel alone gave significant clinical results. Procter & Gamble did not consider this to be an acceptable reference to support the claim as the licensed indication for Elyzol was "the treatment of chronic periodontal disease as an adjunct to conventional therapy".

Procter & Gamble stated that in the field of periodontal treatment, conventional therapy was universally accepted as scaling and root planing, ie the mechanical process of removing calculus and bacteria from the periodontal pocket. It was clear that the study run by Stelzel *et al* did not use Elyzol according to the particulars of the product licence, ie Elyzol was not used in an adjunctive manner following scaling and root planing. Consequently Procter & Gamble questioned the adequacy of the reference to support the claim.

Procter & Gamble stated that general dental practitioners would assume on reading the claim that the "significant clinical result lasting up to 18 months" related to adjunctive use of Elyzol after scaling and root planing versus scaling and root planing alone. This was clearly not the case and, given that it was unreasonable to expect all general dental practitioners to read the full supporting reference for the claim, Procter & Gamble submitted that practitioners would consequently be misled as to the efficacy of Elyzol in accordance with its product licence. Procter & Gamble pointed out that in response to its concerns regarding the validity of the Stelzel study, Dumex had defined adjunctive, in relation to the use of Elyzol, as an adjunctive therapy to scaling

and root planing, as a time period of up to two years. A copy of the correspondence was enclosed.

Procter & Gamble stated that this definition of adjunctive therapy was completely unacceptable to itself and, it submitted, periodontal experts. Further Procter & Gamble pointed out that in the exclusion criteria for the Stelzel study, patients who had received supragingival scaling up to six months prior to the study were specifically excluded thereby demonstrating that the study relied upon to support the claim was actually designed to avoid the use of Elyzol in accordance with the licensed indication.

RESPONSE

Dumex pointed out that the claim for Elyzol Dental Gel had been running in all of its literature, including advertising, exhibition displays, mail shots, detail aids, etc for over two years. During this time it had communicated with the universe of dental practitioners in the UK a consistent message without a single reported complaint, concern, objection or misunderstanding of the message.

In relation to the claim at issue, Dumex pointed out that in detailed correspondence with Procter & Gamble it had continued to point out its position which it believed was entirely justifiable and which in no respect did, nor sought to, contravene the Code. Procter & Gamble's assertion that Dumex was promoting outside of the licensed indication and seeking to intentionally or unintentionally mislead clinicians was, submitted Dumex, misguided.

Dumex noted that the licensed indication for Elyzol Dental Gel was "to be used in the treatment of chronic periodontal disease as an adjunct to conventional therapy". It noted Procter & Gamble's assertion that the reference, Stelzel M *et al* (1994), did not support the licensed indication. Dumex did not agree with this submission.

Dumex noted Procter & Gamble's view that "in the field of periodontal treatment conventional therapy is universally accepted as scaling and root planing ..." and "It is clear ... did not use Elyzol according to the particulars of the product's licence, ie Elyzol was not used in an adjunctive manner" following scaling and root planing. Dumex did not agree with this statement and submitted that this statement represented the major departure point between itself and Procter & Gamble. Dumex could see no evidence that conventional therapy was universally accepted as root planing and scaling when related to the treatment of periodontal disease.

Dumex submitted that the treatment of periodontal disease was complex and of multi-faceted aetiology, requiring a comprehensive approach to treatment planning and an open minded view as to which treatment rationale was best suited to individual patients. To state that "conventional therapy is universally accepted as scaling and root planing" was a gross over simplification.

Conventional therapy, submitted Dumex, might include patient oral hygiene instruction, patient motivation, subgingival irrigation, scaling and root planing, antibiotic treatment (systemic or topical), open flap surgery and debridment, guided tissue regeneration. In addition patients would be placed on a maintenance and recall programme following stabilisation of the disease where repeat of some or all of the above might be necessary.

Dumex submitted that in the study by Stelzel *et al*, to claim that Elyzol was not used in accordance with the particulars of the product licence demonstrated a misunderstanding of the disease, the product licence indication and the study itself.

Dumex referred to the statement by Procter & Gamble that "Elyzol was not used in an adjunctive manner following scaling and root planing...". Dumex referred to one of its letters to Procter & Gamble in which it pointed out that in the study by Stelzel *et al* the patients were clearly defined as being recall patients and in the inclusion criteria for the study it clearly stated that "the patients had undergone subgingival scaling between 6 and 24 months before the start of the treatment". In this study Elyzol Dental Gel had been used within its licensed indication, ie for the treatment of periodontal disease as an adjunct to conventional therapy and specifically as an adjunct to treatment of patients who had previously been scaled and root planed.

Dumex drew attention to the differences between the product licence indications for Elyzol Dental Gel and the Procter & Gamble product Periochip. Whereas "Elyzol Dental Gel is to be used in the treatment of chronic periodontal disease as an adjunct to conventional therapy", the licensed indication for Periochip was "The treatment of chronic periodontitis. It should be used as an adjunct to conventional scaling and root planing in pockets of 5mm or greater, it may be used for repeated maintenance treatment until sufficient clinical benefit is obtained". Dumex pointed out that the Periochip licence was specifically as an adjunct to conventional scaling and root planing. The Elyzol Dental Gel licence was as an adjunct to conventional therapy in chronic periodontal disease. Dumex submitted that Elyzol had a broader licensed indication and believed that this might, in part, be a contributor to the confusion on the part of Procter & Gamble.

Dumex referred to the submission by Procter & Gamble that 'general dental practitioners will assume on reading the claim in question that the "significant clinical result lasting up to 18 months" relates to adjunctive use of Elyzol after scaling and root planing versus scaling alone'. Dumex stated that it could not understand the concerns of Procter & Gamble to whom it had already pointed out in correspondence that the clinical study clearly showed a significant clinical result and that the significant result was on recall and previously scaled and root planed patients.

Dumex referred to Procter & Gamble's claim that it "believes practitioners will consequently be misled as to the efficacy of Elyzol in accordance with its product licence". Dumex referred the Panel to a letter from an NHS consultant in dental public health who was dental advisor to Dumex and specifically to the comments related to "Conventional therapy, and the general dental practitioners viewpoint" and "An understandable UK definition of periodontal treatment" (see below). Dumex then referred the Panel to the Wilkerson Group Report

which was a review of the UK periodontal disease and treatment market before launching Elyzol Dental Gel in 1993.

Dumex noted the submission by Procter & Gamble that Dumex had defined adjunctive, in relation to the use of Elyzol as an adjunctive therapy to scaling and root planing, as a time period of up to two years. Dumex submitted that this was clearly a misinterpretation of its stance which it had outlined exhaustively in its letter of response. Dumex referred the Panel to the letter from its dental advisor (see below).

Dumex stated its belief that its definition of adjunctive therapy was perfectly acceptable to the periodontal profession as it related to Elyzol Dental Gel's licensed indication. Dumex submitted that it had gone to great lengths to enable Procter & Gamble to understand the parameters of the study in question and how it was performed on previously scaled and root planed patients.

To emphasise Procter & Gamble's misunderstanding of the study and the disease area, Dumex drew the Panel's attention to the following statement by Procter & Gamble namely, "Further, we note that in the exclusion criteria for the Stelzel M *et al* study patients who had received supragingival scaling up to six months prior to the study were specifically excluded thereby demonstrating that the study relied upon to support the claim in question was actually designed to avoid the use of Elyzol in accordance with the licensed indication".

Dumex pointed out that the exclusion criteria stated "...treatment with antibiotics in the 6 months preceding the study, periodontal treatment (apart from supragingival scaling) in the 6 months preceding the study...". This meant that contrary to Procter & Gamble's interpretation, people who had been supragingivally scaled up to six months before the study were included. This would be considered correct in all studies of this nature as supragingival scaling was part of good periodontal maintenance therapy and was completely distinct from subgingival scaling and root planing which was what Procter & Gamble referred to as scaling and root planing when they were discussing periodontal treatment.

As well as the letter from its dental advisor, Dumex submitted a letter from the international medical director of Dumex-Alpharma.

The dental advisor to Dumex submitted the following:

1 The Stelzel study

The dental advisor stated that Procter & Gamble's assertion that the Stelzel study demonstrated that both scaling and root planing alone and use of Elyzol dental gel (metronidazole gel) alone gave significant clinical results was a selective and narrow reading of the paper. The advisor noted that the authors had carefully stated that the aim of the study was "to compare the clinical and microbiological effect of ... metronidazole gel ... and subgingival scaling in recall patients over a six month period".

The advisor noted that Procter & Gamble had claimed that metronidazole was not an adjunct when used in this study. The advisor submitted that for this to be correct, the patients treated with metronidazole would have received no other periodontally-related treatment during the study or for a reasonable time before it.

The advisor stated that Procter & Gamble was wrong in its belief that patients who received supragingival scaling in the six months prior to the study were excluded. The study report stated that those who had had periodontal treatment were excluded apart from those who had had supragingival scaling.

The advisor noted that in fact all the patients included in the study had had subgingival scaling between 6 and 24 months previously. The majority of patients had had their most recent (subgingival) scaling 6-15 months before inclusion with a mean of 12 months and a standard deviation of 5 months. Moreover 83% of the patients had previously received periodontal surgery, at some time within the last 10 years - some as recently as 10 months previously.

The advisor noted that all the patients had also had supragingival tooth cleaning carried out during the study "both at the baseline examination and at the subsequent recall examination when necessary". Patients had also received oral hygiene instruction. The authors noted that "allowance must be made for a possible though slight influencing of our results by these treatment measures".

The advisor said that the Stelzel study was carried out on patients who were already involved in ongoing periodontal treatment, prior to inclusion in the study. Supplementary treatment was also given during the study and the effects of these treatments were discussed by the authors. The patients selected for both treatments were not picked *de novo* but came from a group who had already had treatment, and who had also received supplementary care during the study. The advisor contended that the study described the use of two treatment elements in the ongoing care of patients with periodontal disease. As such it satisfied a reasonable definition of a study of adjunct therapy.

The advisor said that using three separate measures of change; pocket probing depths, bleeding on probing and plaque composition, the study concluded that there was no significant difference between the two groups.

2 Conventional therapy and the general dental practitioner's viewpoint

The advisor noted that Elyzol Dental Gel was licensed for the treatment of chronic periodontal disease as an adjunct to conventional therapy, although at times Procter & Gamble referred to Elyzol's use as an adjunct to scaling and root planing. This was Procter & Gamble's own interpretation but the distinction was important.

The advisor noted that part of Procter & Gamble's complaint depended on identifying a suitable definition of "conventional therapy" and also on matters likely to mislead a general dental practitioner. The advisor considered these two issues together, as the most widespread definition of periodontal treatment was

that used by general dental practitioners, and it was not limited to scaling and root planing, nor indeed to any single modality. It was important to consider what a general dental practitioner would understand as conventional periodontal therapy.

3 An understandable UK definition of periodontal treatment

The advisor stated that most general dental practitioners in the UK still practised wholly or partly within the general dental services of the NHS. NHS dental treatment and remuneration was defined in the Statement of Dental Remuneration (SDR), a schedule of treatment options which had been developed and refined over many years. The language of the SDR was one which many dentists adopted in describing treatment, and the terminology of the SDR provided a good guide to what was considered conventional in NHS dental care.

Section IV of the SDR defined "Periodontal Treatment" and was divided into two main groups - Non-surgical Treatment and Surgical Treatment. Non-surgical treatment included options such as scaling, polishing, oral hygiene instruction, root planing and deep scaling. There were a number of surgical options given.

The advisor said that none of these surgical treatments would be so arcane as to escape the definition of "conventional treatment". However, professional experience and knowledge of the NHS led him to believe that root planing was undertaken much less frequently in the British NHS as a treatment for periodontal disease than simpler forms of treatment. The consultant submitted that the most widely used British definition of periodontal treatment - the SDR - included, but was not limited to, root planing and scaling.

4 Conclusion

The advisor concluded by stating that Procter & Gamble had either misunderstood the definition of "conventional therapy" or had adopted a selectively narrow definition. It had already been shown that the Stelzel study considered the use of metronidazole (Elyzol) in the context of wider periodontal treatment.

The advisor noted that Dumex's promotional materials did not describe 2-stage metronidazole gel as a treatment, but merely as "steps". However, these "steps" when used as an adjunct to conventional therapy (which would be understood by a UK general dental practitioner) did, on the basis of the Stelzel study, give "a significant clinical result". It was not claimed that this result was better than, or a substitute for, scaling and root planing. The advisor said that Dumex's use of references and language was not at odds with its marketing authorisation, and would be easily understood by the majority of UK general dental practitioners.

The international medical director of Dumex Alpharma stated:

The licensed indication granted by the Medicines Control Agency for Elyzol Dental Gel was "An adjunct to conventional therapy in the treatment of chronic periodontal disease in adults".

The medical director stated that in the correspondence between Dumex and Procter & Gamble it appeared that Procter & Gamble interpreted "adjunct to conventional therapy" as meaning that the product could only be prescribed within a limited time period following scaling and root planing.

The medical director submitted that promotion of the product was within the licensed indication based upon review of the available scientific evidence. The licensed indication for Elyzol Dental Gel was granted following clinical efficacy data submitted from 4 clinical studies, the results of which were reported in 3 clinical papers (Klinge *et al*; Ainamo *et al*; Pedrazzoli *et al*). The exact selection criteria, with respect to previous periodontal therapy in these studies were: no scaling performed within the last 3 months prior to inclusion (Klinge *et al*); no periodontal treatment performed within the last 6 months prior to inclusion (Ainamo *et al* and Pedrazzoli *et al*).

From the study by Klinge *et al* no information on previous therapy was available. In the studies reported by Ainamo *et al* 57% of patients had previous periodontal treatment 6-24 (36) months prior to inclusion (some had received treatment several years previously). In the study by Pedrazzoli *et al* 37% had previous periodontal treatment 0.6-15 years median 7 years) prior to inclusion. The internal analysis of the data from Ainamo *et al* indicated that treatment outcome was not better in patients that had received previous therapy compared to patients that had not received previous therapy.

The medical director submitted that no studies had been performed with immediate concomitant scaling and root planing and Elyzol Dental Gel treatment. Thus the available scientific information indicated that the time limitations of "adjunctive" (when interpreting scaling and root planing only as being conventional therapy) could range from 3-24 months or more.

The medical director stated that in a paper by Stelzel M *et al* (1997) (which was an 18 month follow-up study to the abstract presented in 1994) which Procter & Gamble claimed was outside the licensed indication the inclusion criteria were tightened compared to the earlier studies and previous scaling and root planing was mandatory, with limits from 6-24 months prior to inclusion. The medical director submitted that this study complied more closely with the licensed indication than those studies upon which the licence was granted.

The medical director stated that scaling and root planing was commonly used for the removal of subgingival calculus. Evidence suggested that once scaling and root planing has been performed and a good oral hygiene and maintenance program was undertaken, the positive effects might be long lasting. Data from the Stelzel *et al* (1997) study clearly showed that the effect of scaling and root planing (and Elyzol Dental Gel) might last for 18 months. When no subgingival calculus was present adjunctive periodontal treatment which might include Elyzol Dental Gel seemed a reasonable treatment regimen.

PANEL RULING

The Panel noted that the Elyzol Dental Gel data sheet stated that it was to be used in the treatment of chronic periodontal disease as an adjunct to conventional therapy. It was to be administered into the periodontal pocket on day 0 and day 7 of the treatment.

The Panel noted that adjacent to the claim at issue was a picture illustrating the method of application of Elyzol Dental Gel into the periodontal pocket.

The Panel was of the opinion that a general dental practitioner might reasonably infer that the claim "Two simple steps gives a significant clinical result lasting up to 18 months..." referred to the dosage of Elyzol Dental Gel or equally, to the use of Elyzol Dental Gel as an adjunct to conventional therapy.

The Panel did not accept Procter & Gamble's view that conventional therapy was defined as scaling and root planing only. In this regard the Panel noted that the NHS Statement of Dental Remuneration for General Dental Services listed a range of surgical and non-surgical treatment options.

The Panel noted that the aim of the Stelzel study was to compare the topical application of metronidazole 25% dental gel with subgingival scaling. Thirty patients with moderate to severe adult periodontitis were selected at random from the recall pool of the department of periodontology of a German University. The patients were included in the study if they had at least one pocket with an initial probing depth of 5mm or more that showed bleeding on probing and had undergone subgingival scaling between 6 and 24 months before the start of treatment. Exclusion criteria included treatment with antibiotics in the 6 months preceding the study and periodontal treatment (apart from supragingival scaling) in the 6 months preceding the study. Oral hygiene instruction was given on day 21. Each patient received both gel application and scaling in parallel, in two randomly selected quadrants of the mouth. 202 teeth were treated with dental gel and 176 with subgingival scaling.

The Panel did not agree with the submission by Procter & Gamble that the study demonstrated that the use of Elyzol Dental Gel alone and the use of scaling and root planing alone gave significant clinical results. The Panel noted that whilst the purpose of the study was to compare these two treatments, all patients included in the study had undergone previous subgingival scaling. The Panel noted that the majority had their most recent subgingival scaling 6-15 months (mean 12 months) prior to inclusion in the study and all patients were involved in ongoing periodontal treatment. In the Panel's view the introduction of Elyzol Dental Gel to these patients constituted adjunctive therapy in the context of ongoing periodontal treatment. The Panel considered that the product was being used within its licensed indication. The claim was not misleading. The Panel therefore ruled no breach of Clauses 3.2 and 7.2 of the Code.

Complaint received **14 August 1997**

Case completed **3 December 1997**

CASES AUTH/604/8/97 AND AUTH/605/8/97

PHARMACEUTICAL ADVISER AND PRESCRIBING MANAGER v ASTRA

Provision of road atlas

A pharmaceutical adviser and a prescribing manager complained separately about a mailing sent by Astra offering a complimentary road atlas.

The Panel did not accept that a road atlas was relevant to a health professional's work and ruled a breach of the Code.

These cases concerned a mailing sent by Astra Pharmaceuticals Ltd. The mailing included a reply paid card (ref BTH 971944D) which offered a complimentary road atlas.

COMPLAINT

Case AUTH/604/8/97

A pharmaceutical adviser at a health authority pointed out that Clause 18 of the Code stated that gifts must be inexpensive and relevant to the recipient's work. The complainant thought that a road atlas of Britain was not relevant to work.

Case AUTH/605/8/97

A prescribing manager at a health authority, stated that in her view the offer of the road atlas was inappropriate but she was unsure as to whether it breached the Code of Practice.

Cases AUTH/604/8/97 and AUTH/605/8/97

RESPONSE

Astra pointed out that Clause 18.2 of the Code stated that any gift must be inexpensive and relevant to the recipient's work. Part of a medical professional's commitments included continuing education and updates. As a result this could involve attendance at educational meetings, whether provided by professional organisations or by sponsoring pharmaceutical companies. The company pointed out that the two complainants were prescribing advisers and would very probably also attend national prescribing meetings with their colleagues. Often such meetings involved travel

throughout the UK, outside the vicinity of the medical professional's usual place of work. In addition, in the day to day work of prescribing advisers, at least the whole area of a health authority would be in their remit and they would visit prescribers throughout the area.

Astra stated that each atlas cost £4.45 and as such it was considered to be an appropriate and inexpensive gift.

PANEL RULING

The Panel considered that the road atlas was acceptable as far as cost was concerned as the cost to the company was £4.45 which was within the £5 limit stated in the supplementary information to Clause 18.2 of the Code.

The Panel noted that advice about road atlases had been given in the November 1995 issue of the Code of Practice Review. This stated that the provision of a detailed local map to a general practitioner might be an acceptable gift, but the provision of a large scale atlas was not. The Panel noted the submission but did not accept that the provision of a large scale road atlas was relevant to the practice of medicine or pharmacy. A detailed local map would enable a healthcare professional to find a particular road in order to visit patients at home or to find a surgery whereas a road atlas did not provide such information. The Panel did not accept that a road atlas was relevant to a health professional's work. The Panel therefore ruled a breach of Clause 18.1 of the Code.

The Panel noted that the proposals to amend the Code included adding road atlases to the list of unacceptable promotional aids.

Complaints received 18 August 1997

Cases completed 20 October 1997

CASE AUTH/607/8/97

DOCTOR v PHARMACIA & UPJOHN

Impotence leaflet "It Takes Two"

A doctor complained about a leaflet for patients entitled "It Take Two: A Couples Guide to Erectile Dysfunction" and alleged that it was biased and misleading as it stated with respect to yohimbine that "...there have been no large-scale studies to prove the drug's effectiveness...".

The Panel considered that the statement was not balanced. It gave the impression that there was no data to prove yohimbine's effectiveness whereas there was data to show a significant improvement in the quality of stimulated erections. This was not reflected in the leaflet. A breach of the Code was ruled.

A doctor complained about a leaflet for patients entitled "It Takes Two: A Couples Guide to Erectile Dysfunction". The leaflet stated that it was supported as a service to medicine by Pharmacia & Upjohn. The leaflet gave background information on erectile dysfunction and discussed treatment options. There was a section headed oral therapy in which the efficacy of yohimbine was discussed.

The leaflet was provided by The Impotence Association to enquirers.

COMPLAINT

The doctor alleged that the leaflet was biased and misleading as it stated that with respect to yohimbine "...there have been no large-scale studies to prove the drug's effectiveness...".

The complainant said that yohimbine had been the subject of many very large-scale clinical trials. One of the most recent trials was conducted under the supervision of Dr Alan Riley, one of the trustees of the Impotence Association. The results of this clinical trial had been published and showed a high percentage of success while the leaflet suggested otherwise.

RESPONSE

Pharmacia & Upjohn confirmed that the leaflet was a guide for patients and partners about erectile dysfunction. It included a section on erectile dysfunction treatments. This section of the leaflet included top line information on changing habits, hormone medications, professional counselling, vacuum devices, injection therapy, penile prostheses, surgical treatment and oral therapy. Pharmacia & Upjohn pointed out that in the paragraph about oral therapy on page 7 of the leaflet, yohimbine was mentioned as a naturally occurring product which had been used for many centuries and which some men found helpful.

Pharmacia & Upjohn submitted that the sentence at issue "While there have been no large scale studies to prove the drug's effectiveness, a small percentage of men report it to be helpful for impotence" reflected available information on yohimbine. The company understood that the study by Dr Riley was indeed the largest ever published controlled study with this product and included only 61 patients. This was the same study and publication which were referred to by the complainant. Pharmacia & Upjohn submitted that this was not a large scale study and indeed not large enough to conduct a complete analysis. The company pointed out that the authors of the study stated "There were too many missing data after 12 weeks to allow meaningful analysis". Furthermore, "Not all patients completed diary cards and where an attempt had been made to complete them there was much missing information. The data from the diary cards are therefore not reported". Thus, submitted Pharmacia & Upjohn, it saw no reason to question the findings of the study but would agree with the authors of the study that not enough patients had been included.

In summary Pharmacia & Upjohn believed that the

statement at issue was factually correct.

Pharmacia & Upjohn pointed out that yohimbine was not a licensed medicine but available for purchase at herbal medicine outlets. The information on yohimbine was included in the leaflet on advice from The Impotence Association since some men did find the product useful, thus the statement in the leaflet "...a small percentage of men report it to be helpful for impotence".

PANEL RULING

The Panel noted that the study by Riley was a placebo controlled randomised cross over study. Patients received either yohimbine or a placebo for eight weeks after which the treatment was crossed over for a further eight weeks. Patients were assessed at four week intervals. The results section stated that there were too many missing data after twelve weeks to allow meaningful analysis.

Seventy patients were recruited into the study and at the end of twelve weeks there was data on sixty one. The discussion section stated that a substantial minority of patients showed no response to treatment with yohimbine. Yohimbine had a beneficial effect on stimulated erections in a group of men complaining of erectile inadequacy of mixed aetiologies. No effect was found on morning or spontaneous erections. The study concluded that the results, when considered in conjunction with previously published studies, would suggest that yohimbine was a worthwhile treatment for patients with erectile inadequacy. The authors suggested that further studies were required to determine optimal dosing regimens and to identify those patients most likely to respond to therapy.

In the Panel's view the study by Riley had shown some benefit. The paper referred to other studies which had demonstrated benefits for yohimbine although these were not available to the Panel.

The Panel considered that the statement in the leaflet that "...there have been no large-scale studies to prove the drug's effectiveness..." was not balanced. It gave the impression that there were no data to prove its effectiveness whereas there was data in the Riley study to show a significant improvement in the quality of stimulated erections. This was not reflected in the leaflet. A breach of Clause 7.2 was ruled.

Complaint received 21 August 1997

Case completed 1 December 1997

CASE AUTH/608/8/97 *NO BREACH OF THE CODE*

DOCTOR v BOEHRINGER INGELHEIM

Letter in Prescriber

A doctor alleged that a letter published in Prescriber from the director of medical operations at Boehringer Ingelheim was disguised promotion as it covertly promoted Mobic, a Boehringer Ingelheim product, an advertisement for which appeared in the same issue of the journal. The letter was presented as a contribution to an ostensibly purely scientific debate in the editorial.

The Panel noted that replies made in response to specific communications whether of enquiry or comment including letters published in professional journals were exempt from the Code if they related solely to the subject matter in question and were not promotional in nature. The letter the subject of complaint had been written in response to an article which included reference to the issue of costs associated with unwanted adverse reactions and the safety profile of preferential COX-2 inhibitors. The letter dealt with the occurrence of gastrointestinal complications with ibuprofen and the tolerability of newer NSAIDs such as meloxicam (Mobic). The Panel considered that the letter was not unreasonable and did not constitute promotion. No breach of the Code was ruled.

Upon appeal by the complainant, the Appeal Board considered that the letter was not unreasonable. It did not constitute disguised promotion. The Appeal Board confirmed the Panel's ruling that the Code had not been breached.

The letter the subject of complaint was from Dr Gary Lapham, Director of Medical Operations, Boehringer Ingelheim Limited, and had been published in Prescriber on 19 August 1997. It was entitled "Ibuprofen GI toxicity" and was in response to an article by Dr A Avery (Prescriber, 5 July) which had examined prescribing performance indicators for non steroidal anti-inflammatory drugs (NSAIDs). The article outlined the rationale for developing prescribing performance indicators and discussed how a measure of the range of medicines prescribed could be applied to NSAID prescribing. The article stated that it was "... difficult to choose between NSAIDs on grounds of effectiveness. However, with respect to safety, ibuprofen appears to have fewer serious side-effects than other NSAIDs". The letter from Boehringer Ingelheim stated:

"... the perception of low risk of serious gastrointestinal complications with ibuprofen seems to be attributable mainly to the low doses of drug used in general practice. In higher doses (beyond 1600mg) ibuprofen is associated with a similar risk to other NSAIDs.

Furthermore the prescription of newer NSAIDs such as meloxicam (Mobic) - with evidence of improved gastrointestinal tolerability versus diclofenac - may reduce the need for additional concomitant medication used to treat gastrointestinal side-effects."

The statement regarding Mobic's improved gastrointestinal tolerability versus diclofenac was referenced to work in press.

COMPLAINT

The complainant alleged that the letter covertly promoted Mobic (adding that the same issue of Prescriber carried an advertisement for Mobic). He noted that Dr Lapham referred to unspecified evidence "in press" to support the claim in his letter. The complainant considered that the letter amounted to disguised promotion, it was presented as a contribution to an ostensibly purely scientific debate in the editorial matter of Prescriber.

RESPONSE

Boehringer Ingelheim stated that the original article to which Dr Lapham's letter related appeared in Prescriber 5 July 1997 and was entitled "Prescribing Performance Indicators for NSAIDs". The article discussed the use of performance indicators for prescribing in general practice whilst recognising the issue of unwanted side-effects as a limiting factor in achieving the goal of "quality care". Dr Avery raised the issue of "rational prescribing of NSAIDs", and made the point that "It is difficult to choose between NSAIDs on grounds of effectiveness" but with reference to safety stated that "... ibuprofen appears to have fewer serious side-effects than other NSAIDs ...". These issues prompted the response made by Dr Lapham in a letter to the Editor submitted on 22 July 1997 and published (unamended) in Prescriber on 19 August 1997.

Boehringer Ingelheim submitted that contrary to the opinion of the complainant, who accused Dr Lapham of covert promotion of Mobic, the letter represented a balanced, scientifically credible contribution to the scientific debate on the rational prescription of NSAIDs. While Dr Lapham agreed with Dr Avery's comments that "it is difficult to choose between NSAIDs on the grounds of effectiveness" he responded that "the perception of low risk of serious gastrointestinal complications with ibuprofen seems to be attributable mainly to the low doses of drug used in general practice. In higher doses (above 1600mg), ibuprofen is associated with a similar risk to other NSAIDs". In his response, Dr Lapham cited the paper by Henry *et al* (1996) which compared the relative risk of serious gastrointestinal complications reported with individual NSAIDs. The paper gave the results of an extensive, collaborative meta-analysis conducted by way of a Medline CD ROM search for the period 1985 to 1994 inclusive. The search was supplemented by a review of previously published material and an update of published results from authors' published data.

Furthermore, original authors were asked for a list of unpublished work. Thus, Boehringer Ingelheim submitted that the paper by Henry *et al* represented a significant and authoritative reference upon which Dr Lapham based his statements.

Boehringer Ingelheim noted that the article by Dr Avery provided a worked example of how PACT data allowed the percentage of prescriptions for the top five most frequently prescribed NSAIDs in the practice to be calculated. Amongst the listed NSAIDs were both diclofenac and meloxicam. Dr Avery's view in relation to the so-called preferential COX-2 inhibitors was that "Although preferential COX-2 inhibitors would appear to have a promising safety profile, further research evidence is needed before they can be considered as first-line treatment in general practice. With respect to cost, ibuprofen and other NSAIDs that are available generically are cheaper than most brand name products".

Boehringer Ingelheim stated that the second part of Dr Lapham's letter referred to the prescription of newer NSAIDs, such as meloxicam - citing evidence of improved gastrointestinal tolerability versus diclofenac. Bearing in mind Dr Avery's comments relating to the (indirect) costs associated with poor prescribing, including side-effects, Dr Lapham commented that "... newer NSAIDs such as meloxicam (Mobic) - with evidence of improved gastrointestinal tolerability versus diclofenac - may reduce the need for additional concomitant medication used to treat gastrointestinal side-effects". Recent reviews by Bateman *et al* (1994), Langman *et al* (1994) and Rodriguez *et al* (1994) identified diclofenac as a drug which ranked second only to ibuprofen in terms of its gastrointestinal safety profile, based on results via the Yellow Card System (Bateman *et al*) and independent hospital (Langman *et al*) and general practice (Rodriguez *et al*) epidemiological studies respectively. In this context a large study comparing diclofenac and meloxicam which demonstrated an improvement in gastrointestinal tolerability when comparing these two medicines, was of interest to prescribers. The study was as yet unpublished, but added significant credibility to the scientific debate on the use of "preferential" COX-2 inhibitors in the management of rheumatic disorders.

Boehringer Ingelheim contended that in responding to Dr Avery's original article, Dr Lapham had provided a clinical viewpoint on the rational prescribing of NSAIDs. Two important issues had been raised within the response, namely the perception of low risk of serious gastrointestinal complications with ibuprofen, which was a dose related phenomenon, such that higher doses of ibuprofen were associated with a similar risk to other NSAIDs. Secondly, in determining the true cost of NSAID prescribing, it was insufficient to merely look at the direct cost of NSAIDs. Indirect costs accruing on gastrointestinal intolerance were relevant for this class of medicine. Thus reference to a new NSAID with an improved gastrointestinal tolerability profile was of clinical interest to prescribers.

Boehringer Ingelheim stated that Dr Lapham's letter therefore added a verifiable contribution to the debate raised by Dr Avery's original article. The company noted that Dr Lapham had received no requests for the data on file relating to the comparison between meloxicam and diclofenac mentioned in the letter - data which fully substantiated the comments made in relation to improved gastrointestinal tolerability with meloxicam. Boehringer Ingelheim said that the complainant might have been better served by seeking these facts rather than contriving a complaint.

The company refuted the allegation that Dr Lapham's letter represented disguised promotion or that there had been a breach of Clause 10 of the Code.

Boehringer Ingelheim submitted that Dr Lapham's letter was consistent with Clause 1.2 of the Code in that the term 'promotion' "does not include: replies made ... 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

... and are not promotional in nature."

PANEL RULING

The Panel noted that Clause 1.2 of the Code stated that 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 and are not promotional in nature".

The Panel noted that the article by Dr Avery outlined the rationale for developing prescribing performance indicators. One of the reasons given was that they encouraged good prescribing, the converse being that poor prescribing was associated with costs including those connected to unwanted side-effects. Dr Avery noted the wide choice of NSAIDs available and stated that "In selecting which of these drugs to use it is important to take account of effectiveness, safety, costs and patient choices".

The Panel noted that in the article Dr Avery stated that it was difficult to choose between NSAIDs on the grounds of effectiveness but in terms of safety ibuprofen had fewer serious side-effects than other agents. The author then went on to state that "Although preferential COX-2 inhibitors would appear to have a promising safety profile, further research evidence is needed before they can be considered as first line treatment in general practice. With respect to cost, ibuprofen and other NSAIDs that are available generically are cheaper than most branded products".

The Panel noted that although the article by Dr Avery was chiefly concerned with the mechanics of performance indicators with respect to NSAIDs as opposed to which NSAID to choose, the author had referred to the issue of costs associated with unwanted adverse events and the safety profile of preferential COX-2 inhibitors. In the circumstances the Panel considered that the letter from Dr Lapham was not unreasonable. It did not constitute disguised promotion and no breach of Clause 10.1 of the Code was ruled.

APPEAL BY THE COMPLAINANT

The complainant said that the middle paragraph of Dr Lapham's letter was indeed consistent with Clause 1.2 of the Code, but this was not the case with the third paragraph, in particular the phrase "... with evidence of improved gastrointestinal tolerability versus diclofenac ..." which was referenced to work "In press".

The reference to unspecified material "in press" did not amount to a "verifiable contribution" (a Boehringer Ingelheim claim) to the debate raised by Dr Avery's article. It was normal good practice to specify at least the journal for all citations to material in press, and usually the authors and title as well. The only details that could not be given for such material were the volume and page numbers, and perhaps the year. These details would indicate that the material had been accepted by an editor, and perhaps that it had been refereed independently. Lack of any detail left readers in doubt about the quality of the data. This was often the case with promotional material citing "data on file".

Boehringer Ingelheim said that Dr Lapham received no request for the data on file, but his letter mentioned no "data on file", and included no offer to supply the material cited as "in press".

The complainant asked that the matter be reconsidered. It seemed to him that the test to be applied was whether the material complained of could be considered promotional by an ordinary well informed reader, not whether there was or was not an intention to promote. The expression "disguised promotion" might seem to imply an intention to disguise it, but the complainant believed that intention in this context could not be proved and should be considered irrelevant. If there was reasonable doubt as to whether a phrase or a citation was promotional, then the complaint should be upheld.

RESPONSE FROM BOEHRINGER INGELHEIM

Boehringer Ingelheim said that the two issues now raised by the complainant were:

1 Whether the reference to as yet unpublished clinical data in Dr Lapham's letter was a verifiable contribution to the debate raised by Dr Avery's article.

2 Whether the material complained of could be considered promotional.

Boehringer Ingelheim submitted that publication of clinical data always took time to achieve yet the company had a responsibility to refer to such unpublished data where clinically relevant and, in particular, for example, in submission to regulatory authorities for the purpose of licensing. In this instance, Dr Lapham's identity and his association with Boehringer Ingelheim were made clear and therefore the reader of his published letter could easily have made contact with him and obtained a copy of the unpublished report. Had the complainant done this, he would have had no difficulty in verifying the data. They were derived from studies that were performed to expected standards of excellence with statistically valid design, appropriate clinical monitoring and audit and detailed analysis.

These studies provided abundant evidence that meloxicam (Mobic) had improved gastrointestinal tolerability compared with widely prescribed NSAIDs. In addition, analysis of the earlier randomised clinical trials database with respect to gastro-intestinal events had shown that meloxicam was cost-saving in comparison with diclofenac. This was the relevance of Dr Lapham's contribution to the scientific debate in the columns of the Prescriber. His knowledge of unpublished clinical information on meloxicam added to the overall review by Dr Avery. The information on Mobic provided by Dr Lapham in his Prescriber letter fell a long way short of that which "an ordinary, well informed reader" would consider sufficient to induce "the prescription, supply, sale or administration of its medicines", as "promotion" was defined in Clause 1.2 of the Code of Practice.

In conclusion, Boehringer Ingelheim submitted that:

- The clinical data on Mobic referred to in Dr Lapham's letter were verifiable and were relevant to Dr Avery's review.

- Dr Lapham's letter was a contribution to scientific knowledge on NSAIDs and was not of promotional intent.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant noted that although reference to unpublished clinical data in Dr Lapham's letter described the material as "in press", the response named neither the journal nor the authors of the paper, suggesting that it had not in fact been accepted by a journal. As the complainant had noted, Dr Lapham did not offer to supply the material cited.

The "MELISSA Preliminary Clinical Trial Report 1996" attached to Boehringer's response contained insufficient information to allow critical appraisal. It included no methods section, almost nothing about the huge population studied, how many centres contributed in which countries, or the variation found between countries/centres. No rationale was presented for giving a constant daily dose of NSAID to patients with osteoarthritis for 28 days - treatment that many physicians would consider questionable. Many significance tests were reported, but the clinical significance of the differences found could not be assessed.

The complainant accepted Boehringer Ingelheim's statement that Dr Lapham's letter had no promotional intent, but, as he had said in his appeal, this seemed irrelevant. The complainant also agreed that Dr Lapham's letter on its own would probably not induce anyone to prescribe Mobic, but, in his view it strongly reinforced other promotion of the drug, and therefore fell within the definition in Clause 1.2 of the Code.

APPEAL BOARD RULING

The Appeal Board considered that the letter from Dr Lapham was not unreasonable. It did not constitute disguised promotion. The Appeal Board upheld the Panel's ruling of no breach of Clause 10.1 of the Code.

The appeal therefore failed.

Complaint received **21 August 1997**

Case completed **13 November 1997**

CASE AUTH/609/8/97

NO BREACH OF THE CODE

CONSULTANT IN PHARMACEUTICAL MEDICINE v SANOFI WINTHROP

Journal advertisement for Tridestra

A consultant in pharmaceutical medicine complained about an advertisement for Tridestra issued by Sanofi Winthrop.

The Panel ruled no breach with regard to an allegation that the statement "Periods are like in-laws, the less they come round the more I like them" was tasteless and offensive and fell below the standards set for the promotion of medicines. In the Panel's view it was unlikely to cause offence to the majority of the audience.

The Panel did not accept that the phrase "And fewer periods a year surely means less hassle" used a hanging comparison. It was clear that the comparator was monthly periods and no breach was ruled. The Panel also ruled no breach of the Code with regard to an allegation that the advertisement was misleading as it equated hormone withdrawal with a normal menstrual period. The words menstruation and periods were commonly used by clinicians and patients when referring to the bleed associated with hormone replacement therapy.

The Panel did not accept an allegation that the statement "And give them more of what they want by giving them less of what they don't" diluted concern about the long term increased risks of thromboembolism and breast cancer. In the Panel's view the statement would be read in the general context of the advertisement, as referring to the number of periods a year. No breach of the Code was ruled.

A consultant in pharmaceutical medicine complained about an advertisement for Tridestra (ref TRI/97/043a) issued by Sanofi Winthrop Limited which appeared in Doctor, 14 August 1997.

1 Statement "Periods are like in-laws, the less they come round the more I like them"

COMPLAINT

The complainant alleged that this derogatory reference to in-laws was in breach of Clause 9.1 of the Code as it was tasteless and offensive and fell below the standards set for the promotion of medicines which should be higher than those which might be acceptable for general commodities.

RESPONSE

Sanofi Winthrop pointed out that Tridestra was the first, and currently the only, sequential hormone replacement therapy (HRT) which offered perimenopausal women, who wished to take HRT, four periods a year as opposed to the traditional thirteen periods associated with the monthly sequential preparations. Monthly preparations had been widely used and formed the mainstay of treatment in this group of women (continuous combined, or so called "period-free" HRTs were advised for postmenopausal women as they were unsuitable for use in the perimenopause or within 12 months of the last menstrual period).

It had long been recognised that the level of compliance with HRT was low with 70% of women who started on HRT stopping therapy within one year. Benefits from the licensed indication, namely the prevention of menopausal

symptoms and the prevention of osteoporosis, would be reduced with lower compliance as the benefits of HRT for these indications increased with prolonged duration of use.

Sanofi Winthrop submitted that in surveys to investigate why compliance was poor, the issue of frequent bleeds was cited as one of the most common reasons for discontinuing therapy. Studies suggested that if women were given the choice of less frequent periods with their HRT this might aid compliance. This was reflected in the summary of product characteristics (SPC) for Tridestra which stated that the three monthly cycle was likely to be more acceptable to this group of women.

Sanofi Winthrop submitted that it was this important patient preference and compliance issue which the advertisement sought to address. It reminded the healthcare professional that frequent periods on sequential HRT were an issue to the patient and that given a choice the majority of women were likely to find fewer periods more acceptable.

Market research was performed during the development of the campaign, initially with 29 GPs who were asked to comment in depth on a series of different proposals including the one finally selected. A smaller range of the more successful advertisement concepts were then tested in greater detail with a further 15 GPs. Both pieces of research contained a representative mix of male and female doctors of mixed ages and racial background. The relevant market research summaries were provided which, the company submitted, reflected the generally positive response the advertisement had with doctors. They described how the humour element added to its high appeal, that it attracted attention and evoked empathy as it described a common complaint/joke but that did not detract from the serious message. The advertisement was considered to be patient based and concentrated on the fewer periods associated with Tridestra.

Sanofi Winthrop stated that the link with fewer periods being potentially better, and fewer visits from the in-laws being potentially better, was easily understood. However good one's relationship was with one's in-laws the concept that their visits could become over frequent was generally appreciated regardless of which side of the line one stood without detracting from the idea of family or being insulting. Sanofi Winthrop drew attention to a typical reaction that "... periods are not the most pleasant of things, you view them less badly if they don't come round so often .... and it's true of in-laws. If they were there kind of living in your house it could get a bit annoying. It tackles it in a very clever and jovial way." Jokes about the "in-laws" did not in any way have the same obnoxious connotations of offensive, racist, sexist or ageist remarks. They were a part of every day banter present in all forms of the media in every day Britain. Sanofi Winthrop stated that while regretting the offence caused to the complainant, it would argue that the overwhelming majority of the readers of the advertisement, in keeping with the majority of healthcare professionals on whom it was tested, would view it as a jovial and lighthearted way of bringing across an important issue in patient compliance and preference with no offence intended or taken.

PANEL RULING

The Panel noted the requirements of Clause 9.1 of the Code that all promotional material and activities must recognise the special nature of medicines and the professional standing of the audience to which they were directed and must not be likely to cause offence. High standards must be maintained at all times.

The Panel accepted that some people might find the advertisement offensive. The Panel considered, however, that the reference to in-laws was unlikely to cause offence to the majority of those who would see it. The Panel therefore ruled no breach of Clause 9.1 of the Code.

2 Statements "And fewer periods a year surely means less hassle in terms of moodiness, inconvenience, and discomfort" and "It's the inconvenience and hassle, every time she has a period, that she dislikes"

COMPLAINT

The complainant alleged that the phrases "gives fewer periods a year" and "surely means less hassle" were hanging comparisons which did not make it clear whether Tridestra was being compared to other HRTs or to taking no treatment at all. Further the complainant alleged that the advertisement equated hormone withdrawal, at the end of each three monthly course of ninety tablets, with a normal menstrual period. The complainant alleged that this was misleading.

A breach of Clause 7.2 of the Code was alleged.

RESPONSE

Sanofi Winthrop stated that Tridestra was described as a perimenopausal HRT offering perimenopausal women just four periods a year. The perimenopause was defined as being the time approaching the menopause with increasingly irregular periods. Period free HRT was generally not recommended for these women until they were 12 months from their last period and defined as postmenopausal because of the frequency of breakthrough bleeding when these preparations were given to younger women. As a result the majority of women in this category were given monthly preparations resulting in 13 periods a year. The tradition and overwhelming popularity of monthly preparations meant that many healthcare professionals did not consider the alternatives and monthly bleeds were taken as the norm for perimenopausal HRT.

Sanofi Winthrop submitted that the advertisement aimed to address the issue by highlighting that the assumed necessity for monthly periods was not the only option for this group of women. The advertisement stated "Tridestra is the only HRT to offer perimenopausal women just four periods a year. And fewer periods surely means less hassle in terms of moodiness, inconvenience, and discomfort".

The company fully accepted that the phrase "fewer periods" was a comparison. It compared the four periods a year with Tridestra with the number of periods which the audience would automatically associate as being usual. Monthly periods, while not necessarily always the

case, would, to the audience it was directed at, be taken as the natural comparator. In an advertisement referring to the frequency of periods with sequential HRT in perimenopausal women, the company submitted that healthcare professionals would automatically take four periods a year as being fewer than the monthly periods associated with normal menstruation or all the other sequential HRTs without the requirement to spell out the fact that periods were generally monthly.

The second alleged hanging comparison was closely related. "Fewer periods a year, surely means less hassle". Sanofi Winthrop submitted that less hassle was associated with the fewer periods for which the comparison had been dealt with above.

Sanofi Winthrop accepted that it was physiologically correct to note that the basis of a withdrawal bleed with HRT differed from normal menstruation in that the decline in progestogen, which precipitated the sloughing of the endometrium, was exogenous rather than endogenous. However, the use of the word "period" or "menstruation" (a period was defined in the concise Oxford English Dictionary as an occurrence of menstruation) to denote hormonal withdrawal was so widespread as to demonstrate acceptance of the similarity to the patient of the two processes. This was reflected in the market research reports where the bleed associated with HRT was referred to as a period by the healthcare professionals rather than as a hormone withdrawal bleed.

Sanofi Winthrop submitted that the words "menstruation" and "period" were used to indicate the bleed associated with the end of the progestogen phase of sequential HRT. It was technically correct to indicate the difference to normal menstruation but this difference was lost on the majority of patients and so the two were used interchangeably by clinicians. Indeed the SPC for Tridestra referred to the bleed as "menstruation" rather than the physiologically specific "hormone withdrawal". Given the current use of terminology including Tridestra's SPC, Sanofi Winthrop submitted it was justified in using the word "period" to clarify the advertisement to the intended audience.

PANEL RULING

The Panel noted that the purpose of the advertisement was to convey to prescribers the fact that Tridestra was associated with only four periods a year. The text of the advertisement concentrated on this issue. The Panel noted that the strap-line was "For confidence, for control, four periods a year". No other topic was discussed.

The Panel accepted the submission from Sanofi Winthrop that in the context of the advertisement the phrase "fewer periods" was comparing the four periods a year with Tridestra with the number of periods which the audience automatically associated as being the usual, these being monthly periods. The Panel decided that it was clear from the context of the advertisement that the comparator was monthly periods. The Panel therefore ruled no breach of Clause 7.2 of the Code.

The Panel noted the submission from Sanofi Winthrop that the physiological basis of a withdrawal bleed with HRT differed from normal menstruation but accepted that the words "menstruation" and "period" were commonly used by clinicians and by patients when referring to the bleed associated with HRT. In the Panel's view it would be unusual for a withdrawal bleed to be referred to in its correct physiological terms. The Panel did not therefore consider that the reference to "periods" in the advertisement was misleading and therefore ruled no breach of Clause 7.2 of the Code.

3 Statement "And give them more of what they want, by giving them less of what they don't"

COMPLAINT

The complainant alleged that the statement "And give them more of what they want, by giving less of what they don't" diluted the concern about the long term increased risks of thromboembolism and breast cancer. It ignored the preliminary data from a study by Cerin *et al* (1996) that there may be an excess risk of endometrial hyperplasia in users of "long-cycle" HRT compared with "monthly bleed" HRT.

A breach of Clause 7.2 of the Code was alleged.

RESPONSE

Sanofi Winthrop stated that with regard to the complainant's view that the advertisement diluted the concern of long term risk of thromboembolism, breast cancer and endometrial hyperplasia with HRT, the phrase at issue in the advertisement was "and give them more of what they want" (ie relief from menopausal symptoms and protection from osteoporosis associated with compliance with therapy) "... by giving them less of what they don't want" (ie hassle, moodiness, discomfort and inconvenience associated with frequent periods). The debate concerning the possible association between thromboembolism and breast cancer and HRT was well recognised by the Medicines Control Agency and in common with all other HRTs appropriate warnings were included in the contraindications and special warnings sections of Tridestra's SPC. Sanofi Winthrop submitted that in the circumstances the prescribing information was the most appropriate place to inform the reader of these issues and not the body of the advertisement.

The reference to the preliminary data from a study by Cerin *et al* was in relation to a letter published in the New England Journal of Medicine in March 1996. No paper had followed which made analysis difficult owing to the limited amount of data provided in the brief letter. The letter made clear that the long cycle HRT used had significant differences to Tridestra. Firstly, only one milligram of norethisterone (equivalent to 10mg of medroxy-progesterone acetate (MPA)) was given compared with 20mg of MPA in Tridestra; secondly, the progestrogen was only given for 10 days in three months compared with 14 days in Tridestra; thirdly, unlike Tridestra there was no placebo phase in the preparation used with the oestrogen being given continuously. Sanofi Winthrop submitted that for these reasons it would not seem appropriate to equate long cycle HRT used by Cerin with Tridestra and it would not be appropriate therefore to make reference to a study which had not been peer reviewed and published and which used a product significantly different from Tridestra.

PANEL RULING

The Panel considered that the statement "And give them more of what they want, by giving them less of what they don't" would be read, in the general context of the advertisement, as referring to the number of periods a year. It did not accept that the advertisement diluted concern about the long term increased risks of thromboembolism, breast cancer and endometrial hyperplasia with HRT as alleged. The contra-indications and warnings were given in the prescribing information. There was no discussion of side effects etc in the main body of the text. Given the content of the advertisement and the comments made by Sanofi Winthrop that the Cerin study used a long cycle HRT which was different to Tridestra, the Panel considered that it was reasonable not to make reference to the Cerin data. The Panel did not accept that the advertisement was misleading in this regard and therefore ruled no breach of Clause 7.2 of the Code.

Complaint received 22 August 1997

Case completed 22 October 1997

CASE AUTH/610/8/97 *NO BREACH OF THE CODE*

RESEARCH ETHICS COMMITTEE v GLAXO WELLCOME

Serevent study

A research ethics committee complained about a study on Serevent. Members of the committee considered that the purpose of the study was to promote Serevent and create a new niche for the product.

The Panel accepted that any study would inevitably have some promotional impact. The Panel considered that the study was being conducted in an attempt to answer a valid scientific question. The Panel did not consider that the study constituted disguised promotion for Serevent and ruled no breach of the Code.

A research ethics committee complained about a study on Serevent (salmeterol) initiated by Glaxo Wellcome UK Limited. The study was a multi-centre, double-blind, placebo-controlled, randomised, parallel group study to investigate whether the addition of Serevent, 50mcg bd or 100mcg bd, shortened recovery time and hence in-patient time for patients hospitalised with an acute severe exacerbation of asthma.

COMPLAINT

A director of health complained on behalf of a research ethics committee which considered that the purpose of the study was essentially promotional in nature and therefore in breach of Clause 10 of the Code.

The research ethics committee noted that the study was designed to detect a reduction in hospital length of stay of 1.5 days in asthmatics still in hospital after 48 hours. The committee questioned the value of this since:

- the average length of stay of the majority of asthmatics was less than 48 hours, those over 48 hours therefore constituted a very small group;
- a reduction of 1.5 days was so short as to call into question whether it could be achieved in practice, and therefore whether this reduction would be of any benefit to the NHS or patients;
- currently, in-patient contracting prices only increased after stays of 28 days; therefore, this type of reduction would not affect contracting prices.

The research ethics committee said that asthmatics could be particularly susceptible to psychological factors, with respect to control of their asthma, and, if they believed the drug had benefited them, rightly or wrongly, they were likely to request this from their GP, particularly since this was started by the hospital and therefore, in their eyes, might be a "better" drug. Parallels might be drawn with the promotion of loss-leaders in hospitals.

The research ethics committee said that should the study show a reduction, even though there would be no apparent benefit, one could imagine the suggestion that all asthmatics admitted to hospital should receive this as standard treatment, thus creating a new niche for salmeterol (Serevent), a well established, long-acting beta-2 adrenoceptor agonist, launched in the late 1980's, and now in need of new areas of use.

In addition the research ethics committee said that there was a lack of detail on the work to be carried out by the investigators. However, it was considered that the sums of money offered to the investigators seemed disproportionate, even taking account of BMA guidelines. Given this, the committee alleged that the study might be in breach of Clause 18.

RESPONSE

Glaxo Wellcome was surprised to receive a complaint about the study, which was scientific, ethical, and designed to fulfil Good Clinical Practice Guidelines.

Glaxo Wellcome submitted that the study was based upon a formal proposal received by the company in October 1994 from a consultant physician who had had many years' experience in both respiratory research and the clinical management of asthma. The consultant had observed that it appeared to be possible to achieve the British Thoracic Society's discharge criteria, following hospital admission for an acute exacerbation of asthma, more quickly if salmeterol was introduced during the recovery phase. The study described was designed to test the consultant's hypothesis. The primary objectives of the study were to determine, in a formal double-blind, placebo-controlled, randomised study whether the addition of salmeterol to a patient's normal hospital

treatment following admission for an acute severe exacerbation of asthma could:

a) lead to reaching the British Thoracic Society (BTS) criteria for discharge (namely peak expiratory flow > 75% of predicted, diurnal variability < 25% and no nocturnal symptoms) earlier.

b) shorten in-patient hospital time.

The study was designed to detect a difference of 1.5 days between the two treatments (placebo and salmeterol).

Glaxo Wellcome said that the duration of hospital stay alone would not have been an appropriate primary end-point as it was necessary to allow a unit to discharge patients either when they fulfilled the BTS criteria or when the physician was satisfied that the patient was ready for discharge. The discharge of patients from hospital, following exacerbations of asthma, needed close cooperation between the hospital and general practitioner services.

Glaxo Wellcome said that the choice of delivery system for the salmeterol, the Accuhaler, reflected the preference of the principal investigator (the consultant physician) who believed strongly in the benefits to patients from using dry powder inhaler devices. The device contained 60 doses and had a dose counter which might help to assess patient compliance during the study. This device would also be used to administer relief salbutamol when required. The study design specifically left the choice of inhaled corticosteroid and its delivery system to the discretion and normal practice of the investigating physicians.

Glaxo Wellcome said that the consultant's centre could not provide sufficient patients for the study (140) to achieve the required statistical power and so he had suggested that he should approach other physicians in the region. Glaxo Wellcome UK had been prepared to provide blinded drugs and some financial support for the study but the consultant had found it impossible to obtain indemnity. Glaxo Wellcome UK took over the management of the study in order to provide indemnity.

Glaxo Wellcome addressed the research ethics committee's complaint that the study was promotional in nature by considering the following:

Length of stay

Glaxo Wellcome said that the length of stay following an admission for an acute exacerbation of asthma would vary depending upon the patient's age, the severity of the asthma and the location. The time of 48 hours was chosen in order to exclude those patients with less severe asthma who would be discharged more quickly and to make sure that the acute phase management was not prejudiced.

Reduction in length of stay

Glaxo Wellcome said that a reduction of 1.5 days had been selected in order to be definitely greater than one whole hospital day, although the time to attainment of BTS criteria for discharge would take priority over the duration of hospital stay when the data were analysed.

The BTS criteria for discharge were designed to protect patients (safety) and to minimise the likelihood of their re-admission to hospital with a further exacerbation of asthma. Re-admission suggested that the patient was again at risk from severe asthma as well as there being resource implications for the hospital service.

In-patient contracting prices

Glaxo Wellcome said that the relevance of "contracting prices" was not immediately apparent. Every day spent in hospital clearly utilised resources and had financial implications, ie there was a measurable cost. The patient might benefit directly by spending less time in hospital, including perhaps an earlier return to work or to caring for children. A possible outcome of the study might be to consider *real* cost implications of patient management and not the artificial structures of "contracting prices".

Susceptibility to psychological factors

Glaxo Wellcome said that the wording of the complaint suggested that the research ethics committee had failed to recognise the purpose of the double-blind, placebo-controlled, randomised parallel group study design - the "gold standard" of clinical research. This was clearly to remove sources of potential bias in the analysis and interpretation of the results, whether the bias might arise from the investigator or the patient. The company was very surprised to read that the complainant felt that a parallel might be drawn with the promotion of loss leaders in hospital.

New niche for salmeterol

Glaxo Wellcome said that the purpose of the study was fully explained in the protocol. It was contradictory to suggest that the study was designed to create a new niche for salmeterol, when the complainant had already suggested that the number of patients likely to fulfil the inclusion criteria was "very small", which hardly represented a commercial venture.

Glaxo Wellcome rejected absolutely the research ethics committee's assertion that the study was promotional and the company did not consider that it was in breach of Clause 10 of the Code.

Remuneration to investigating centres

Glaxo Wellcome said that the patients' information letter contained the statement "Glaxo Wellcome will pay your doctor for the time he/she spends on the study." The total sum paid for each evaluable patient completing the study was £340 and a further breakdown was included in the "letter of agreement". This also covered any administration fee for the 3 month follow-up questionnaire to patients' general practitioners.

Glaxo Wellcome enclosed a copy of the BMA Recommended Investigator Fees from which would be apparent that the sum of £340 was not at all unreasonable when compared with the BMA recommended fee of £126 per hour for participation in clinical trials.

Glaxo Wellcome stated that Section 19 (ii) of the ethics committee's proforma (application form), a completed copy of which was supplied to the Panel, actually stated that the investigator fee would be paid direct to a "trust or

research fund" and not to the researcher. This was in line with Glaxo Wellcome's own Clinical Research Guidelines, Section 2.9, a copy of which was also supplied to the Panel. It was difficult to understand how this arrangement might be a breach of Clause 18 of the Code which covered the question of inducements to prescribe medicines and the provision of gifts to health professionals.

Glaxo Wellcome rejected absolutely the research ethics committee's allegation that the study was in breach of Clause 18 of the Code.

PANEL RULING

The Panel noted that the only clause in the Code relating to clinical trials and the like was Clause 10.2 which required that studies must not be disguised promotion. The Panel accepted that any study would inevitably have some promotional impact but studies must not be such that they were promotional *per se*.

The introduction to the study stated that hospital admissions due to acute severe asthma remained frequent and the length of stay had resource implications for the NHS. The primary aim of the study, therefore, was to determine whether the addition of salmeterol to a patient's normal hospital treatment, following admission for an acute severe exacerbation of asthma, would shorten recovery time and hence time spent as an in-patient. The study was designed to detect a difference of 1.5 days in hospital stay between salmeterol and placebo. In the Panel's view a reduction in hospital stay would have a positive impact on hospital in-patient resources.

The study was to be conducted in approximately 10 centres, each recruiting 10-15 patients. Salmeterol Accuhalers (50mcg), and matching placebo, were provided by Glaxo Wellcome. Patients were not to be given the study medication until they had been in hospital for at least 48 hours. Patients would continue to receive study medication (ie either salmeterol or placebo) until they attended the 14 day post-discharge follow up visit. Patients would have no way of knowing whether the medicine they were receiving was active or placebo.

The Panel noted that the original study documentation stated that it was a double-blind, placebo-controlled, randomised, parallel group study. Only the salmeterol and matching placebo were provided by Glaxo Wellcome. All other therapies were to be provided and prescribed by the hospital as per normal clinical practice. At discharge patients were to be prescribed appropriate asthma therapy, at the discretion of the doctor, with the exception that long-acting beta-2 agonists could not be prescribed as patients continued to take their study medication for another two weeks.

The Panel noted that the protocol had been amended following investigators' meetings for potential investigators to discuss and agree standard asthma therapy for study patients to be used by all participating centres. Patients were initially to be given high dose oral steroids and when the reduction of the oral steroid was started inhaled steroids were to be commenced. The protocol gave a range of doses of beclomethasone dipropionate, budesonide and fluticasone dipropionate which were to be used but stated that the medicine, dose and device selected were at the discretion of the responsible physician. Once entered into the study all patients would be prescribed Ventolin Accuhaler until the end of the study. This was to be supplied by Glaxo Wellcome.

The Panel considered that the study was being conducted in an attempt to answer a valid scientific question. The Panel did not consider that the study constituted disguised promotion for salmeterol and ruled no breach of Clause 10.2 of the Code.

The Panel considered that the payment of £340 was reasonable given that the BMA suggested fee for participation in a clinical trial was £126 per hour. Patients had to be assessed at entry to the trial, discharge from hospital and at a 14 day post-discharge visit. In addition a questionnaire had to be sent to the patient's GP three months after discharge asking for details of any hospital admissions for asthma since completion of the study. The Panel noted that the payments for the study were not given to individual investigators but paid into a trust or research fund. No breach of the Code was ruled with regard to the payments for the study.

Complaint received **29 August 1997**

Case completed **11 November 1997**

CASE AUTH/612/9/97

NO BREACH OF THE CODE

MOLECULES TO MARKET v ASTRA

Provision of diagnostic kits

Molecules to Market complained that Astra was providing physicians with free Helisal diagnostic kits for the detection of *Helicobacter pylori*. It was alleged that this was to promote Astra's eradication therapy. The cost of each kit was greater than that allowed for a promotional aid and it appeared that physicians were being given more than one.

The Panel noted that the kits did not bear Astra's name or that of any of its products. They were provided free of charge by Astra's head office in response to requests from health professionals and there was no evidence of any link between the provision of the kits and the promotion of products. The Panel considered that the supply of the kits would enhance patient care and benefit the NHS and ruled that there had been no breach of the Code.

COMPLAINT

Molecules to Market alleged that the provision of free Helisal diagnostic kits, for the detection of *Helicobacter pylori*, to physicians by Astra Pharmaceuticals Ltd constituted a breach of Clauses 18.1 and 18.2 of the Code.

Molecules to Market alleged that as Astra did not commercially sell the Helisal test its only motivation could be to increase the prescription of its eradication therapy and to protect market share from erosion by Glaxo Wellcome and SmithKline Beecham, in breach of Clause 18.1 of the Code.

Molecules to Market stated that the list price of the Helisal test was £12, which constituted a substantially greater value to the physician than £5. In addition, Molecules to Market alleged that it appeared that more than one kit was being left with the physician per visit, suggesting that the total value of the gift might be at least twice the £12 kit price. Molecules to Market alleged that this was in breach of Clause 18.2 of the Code.

RESPONSE

Astra stated that Molecules to Market had not provided any example from doctors or pharmacists of Astra breaching Clauses 18.1 and 18.2 of the Code. Astra submitted that the Helisal diagnostic kits were not provided as a promotional aid. They did not bear the name of any medicine nor the company name. Astra submitted that Clause 18.2 of the Code did not apply.

Astra submitted that it provided Helisal kits to physicians in accordance with Clause 18.1 of the Code. In this regard the company referred to the supplementary information to Clause 18.1 headed "Provision of Medical and Educational Goods and Services". There was no evidence that the kits had been provided as an inducement to prescribe or buy any medicine.

Astra stated that the Helisal kits were available free of charge to primary and secondary care doctors and practice nurses and were used to ensure the correct diagnosis before commencing on a *H pylori* eradication regime. If patients did not have access to local services physicians often requested Helisal kits from Astra. The kits were all managed by head office and were provided to all those physicians who requested them as a service to the NHS. This was not dependent upon their prescribing habits. Astra submitted that the kits were not related to any particular treatment for *H pylori* and did not bear the name of any medicine or the company name. It was pointed out that there were now several authorized regimes for the eradication of *H pylori*, some of which did not include Astra products. Astra submitted that clearly lansoprazole and Pylorid, which were the basis for some regimes, were not made by Astra and hence there was no link to prescribing its product.

Astra stated that the service was made available due to the growing awareness of the role of *H pylori* in peptic ulcer disease and was provided in response to requests from health professionals. The requests were made by telephone or letter to its head office. Astra submitted that the kits were provided as an ethical service to the NHS to enhance patient care and had been commented on very positively by healthcare professionals. Astra pointed out that the provision of free test kits to doctors might potentially affect the sales of another new test kit on the market. Astra stated that as there was no link with prescribing it did not see how the provision of these kits related to the Code.

Astra confirmed that the service operated with the kits being provided when required; there was no written document to inform health professionals of the availability of the kits. There had been no specific targeting of particular physicians or health professionals, although the service had been used mainly in primary care. The service was provided irrespective of prescribing habits for Losec or any other treatment.

Astra confirmed the cost to the company of a Helisal diagnostic kit and provided the Panel with a copy of the invoice. Astra regarded this as commercially sensitive information which should not be disclosed to the complainant.

PANEL RULING

The Panel noted the supplementary information to Clause 18.1, headed "Provision of Medical and Educational Goods and Services" which stated that it was permissible to provide "...medical and educational goods and services which will enhance patient care or benefit the National Health Service. 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. They must not bear the name of any medicine but may bear a corporate name".

The Panel noted that the kits were provided free of charge by Astra's head office in response to requests from healthcare professionals. There was no evidence of any link between provision of the kits and the promotion of products.

The Panel expressed concern about the absence of documentary evidence to confirm the mechanism by which health professionals were informed about the availability of this service. There was however no evidence that the provision of the kits constituted an inducement to prescribe, supply, administer or buy any medicine as alleged. The supply of the kits would enhance patient care and benefit the NHS. The Panel therefore ruled no breach of Clause 18.1 of the Code.

The Panel noted that the kit did not carry the name of a medicine or the company name. It further noted the company's submission that the kit had not been used as a promotional aid. The Panel therefore ruled no breach of 18.2 of the Code.

Complaint received 2 September 1997

Case completed 23 December 1997

CASE AUTH/613/9/97 *NO BREACH OF THE CODE*

GENERAL PRACTITIONER v WYETH

Zoton advertisement

A general practitioner complained about the use of religious imagery in an advertisement for Zoton. The advertisement featured a doctor who had been ordained as an Anglican priest and pictured her in a church setting. The complainant considered that the crucifixion imagery in the advertisement was entirely unnecessary for the promotion of a secular theme and might be viewed as cynical exploitation of a "higher authority".

The Panel noted that the depiction of the crucifixion was not a prominent part of the photograph but appeared in the background of a church setting. A religious theme was not the basis of the advertisement. The theme was that here was a doctor who had achieved something unusual and of note in her life - becoming ordained. The Panel noted the complainant's concern regarding the use of religious semiology in pharmaceutical advertising but did not consider that in this case it would be a view shared by the majority of the audience. The Panel did not consider that the Code had been breached.

A general practitioner complained about an advertisement for Zoton (ref ZOT696/0697), issued by Wyeth Laboratories, which had appeared in Pulse in June 1997. The advertisement, which was headed 'Out of the Ordinary', featured a colour photograph of an "Anglican Priest. No ordinary doctor" who was identified as Dr Jeanette Meadway. Dr Meadway was in ecclesiastical dress in a church setting. In the background was a stained glass window which depicted the crucifixion. Beneath the photograph were some claims for Zoton followed by, in small print, a disclaimer to the effect that Dr Meadway's involvement in the advertisement was not intended to be an endorsement for the product.

COMPLAINT

The complainant considered that the use of the crucifixion imagery was entirely unnecessary for the promotion of a secular theme. Indeed, it might be viewed as cynical exploitation of a "higher authority". Dr Meadway's small disclaimer was eclipsed by her presence within this promotional opportunity.

The complainant was concerned that this use of religiously sensitive and powerful imagery might subliminally endorse these secular products. The complainant said that there was an increasing tendency in the use of religious semiology in current advertising within the pharmaceutical industry. He had already contacted Wyeth and the Advertising Standards Authority (ASA) regarding the advertisement in question and copies of the correspondence were enclosed.

RESPONSE

Wyeth noted that the main argument put forward by the complainant was that the use of crucifixion imagery was unnecessary for the promotion of a secular theme. In this context the complaint was a general one relating to the use of religious imagery in secular advertising, and not specifically related to the Zoton campaign or the Code. Wyeth noted that in the general context of secular advertising the ASA had already ruled that there was no breach of its standards.

Wyeth referred to the complainant's letter to the ASA in which he had said that his concern was that in the background of the church, but clearly in focus, was a stained-glass window depicting the crucifixion. In the complainant's view this was such a strong symbol in Christian semiology as to cause concern when it was depicted incongruously. Furthermore, the complainant could understand doctors in the Islamic, Jewish and Hindu community feeling uncomfortable about the use of Christian imagery.

Wyeth noted that, as the complainant said, the image of the crucifixion was simply part of the background to the advertisement, rather than being in any way the focus of the advertisement.

Wyeth submitted that throughout the development of the campaign it was careful to select doctors who were 'Out of the Ordinary' for what would reasonably be regarded as positive and laudable achievements. The campaign in no way aimed to link the crucifixion *per se* with the 'Out of the Ordinary' theme. On the contrary, the sub-heading 'Dr Jeanette Meadway. Anglican Priest. No ordinary doctor' was intended to make the link very clearly between Dr Meadway herself and the 'Out of the Ordinary' theme.

Wyeth said that before agreeing to take part in the campaign Dr Meadway had consulted with members of her local Church Authority and also the Bishop of her diocese. Following their discussions, Dr Meadway and her colleagues were not concerned about the use of her

image as depicted, and they were clearly satisfied that the image used would not cause offence to the intended audience.

Wyeth acknowledged that the crucifixion was indeed a strong Christian symbol. However, the only reason that the image of the crucifixion was visible at all was that the photograph of Dr Meadway was taken in her church, which happened to have a stained-glass window depicting the crucifixion behind the pulpit. Wyeth said that to date it had not received any complaints from doctors in the Islamic, Jewish or Hindu communities.

With regard to the complainant's comments regarding the disclaimer, Wyeth submitted that each of the four doctors featured in the 'Out of the Ordinary' campaign had individually approved the wording, size and position of the disclaimer which appeared underneath their image. The disclaimer used in the advertisement in question was as suggested by The Medical & Dental Defence Union of Scotland, which was the defence union to which Dr Meadway belonged.

Wyeth noted that the complainant clearly acknowledged that the Zoton campaign was not the first, nor was it the only, pharmaceutical advertising campaign to include images which might be associated with a particular religion. As already stated, the main argument put forward by the complainant was that the use of religiously sensitive and powerful imagery might subliminally endorse secular products.

Wyeth submitted that the 'Out of the Ordinary' campaign maintained the necessary high standards such that it did not bring discredit upon, or reduce confidence in, either Wyeth, or the pharmaceutical industry as a whole.

Wyeth said that the doctors featured in the 'Out of the Ordinary' advertising campaign, and the settings in which those doctors were portrayed, were carefully selected to avoid causing offence. Wyeth recognised that advertisements were subject to individual doctors' perceptions and that the complainant held strong personal views in the present case. However, this campaign had been published in a wide range of medical journals over a period of some 4 months and Wyeth had received no other complainants. Wyeth submitted that this campaign was not offensive to the medical community at large, or in any particular part. The company did not consider, therefore, that there had been a breach of the Code.

PANEL RULING

The Panel noted that the photograph of Dr Meadway had been taken in the general context of her other role as an Anglican priest. The depiction of the crucifixion was not a prominent part of the photograph but appeared in the background of a church setting. The theme of the advertisement was that here was a doctor who had achieved something unusual and of note in her life - in this case becoming ordained. The religious theme did not form the basis of the advertisement *per se*. The Panel acknowledged the complainant's concern regarding the use of religious semiology in pharmaceutical advertising but did not consider that in this case it would be a view shared by the majority of the audience.

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

Complaint received **17 September 1997**

Case completed **3 November 1997**

CASE AUTH/614/9/97

RHÔNE-POULENC RORER v PHARMACIA & UPJOHN

Fragmin detail aid

Rhône-Poulenc Rorer complained about a detail aid for Fragmin issued by Pharmacia & Upjohn.

In relation to a bar chart depicting the results of a study, Rhône-Poulenc Rorer alleged that the statement that Fragmin had been compared with "...standard cardiovascular medications in current use" had not made it clear that the regimen compared did not include heparin. It was misleading to compare Fragmin with a regimen that did not include heparin and to refer to that regimen as "standard medication". The Panel considered that in the UK heparin was regarded as a standard component of therapy for unstable coronary heart disease. In the Panel's view the majority of readers would assume that "standard medication" would include heparin and the fact it did not meant that a misleading baseline was presented against which to judge comparative efficacy. A breach of the Code was ruled.

Rhône-Poulenc Rorer alleged that a double page heading "Fragmin equals the effectiveness of standard heparin...and facilitates convenient, flexible management" implied that the data on these two facing pages was a comparison with heparin, but this was not so. The Panel considered that, given the headline, most readers would assume that Fragmin was being compared with standard heparin which was not so. The fact that this had been explained in the small print was not acceptable. The Panel considered that the headline together with the presentation of the study data were misleading and a breach was ruled.

Rhône-Poulenc Rorer alleged that the presentation of a table which compared low molecular weight heparin with heparin taken from a study which compared enoxaparin and heparin misled the reader into believing that the data referred to Fragmin. The low molecular weight heparins differed in many respects including different anti-thrombotic activity. It was inappropriate to use data from an enoxaparin study to support dalteparin (Fragmin). The Panel considered that the data had been presented in such a way that readers would assume that it referred to Fragmin which was not so. The presentation was misleading and a breach was ruled.

No breach was ruled in relation to an allegation that the use of data relating to enoxaparin represented the promotion of an unlicensed indication. Enoxaparin was not Pharmacia & Upjohn's product.

Rhône-Poulenc Rorer Limited complained about a detail aid for Fragmin (dalteparin) (ref: P2808) issued by Pharmacia & Upjohn Limited.

1 Presentation of data from the FRISC (Fragmin during instability in coronary artery disease) study

Page 5 of the detail aid featured a bar chart depicting the results of the FRISC study. The text which introduced the chart stated that the study had compared Fragmin with "standard cardiovascular medications in current use". The two bars were labelled "standard medication (including aspirin) ..." and "Fragmin + standard medication (including aspirin) ...". Small text below the chart stated "Concomitant medication used in this trial: aspirin, beta-blockers, calcium antagonists, nitrates". The data presented had been published in The Lancet (Wallentin *et al* (1996)).

COMPLAINT

Rhône-Poulenc Rorer stated that in the labelling of the bar chart it had not been made clear that standard medication did not include heparin. Rhône-Poulenc Rorer considered that heparin was standard treatment for patients with unstable coronary artery disease. To compare Fragmin with a regimen that did not include heparin but to refer to the regimen as "standard medication" was misleading. Rhône-Poulenc Rorer alleged a breach of Clause 7.2.

Rhône-Poulenc Rorer submitted that standard medication for the treatment of unstable angina in the UK included heparin. The data as presented in the Fragmin detail aid suggested that standard medication did not include heparin. Rhône-Poulenc Rorer provided three papers in support of its position. The first from Circulation (Cohen *et al* (1994)) set out the case that anti-thrombotic therapy was beneficial. The second, published in JAMA, (Oler *et al* (1996)) was a meta-analysis where the authors concluded that "The bulk of evidence suggests that most patients with unstable angina should be treated with both heparin and aspirin". The third paper from the New England Journal of Medicine (Cohen *et al* (1997)) opened by stating that "Anti-thrombotic therapy consisting of an intravenous infusion of unfractioned heparin plus oral aspirin represents the current standard of care for patients hospitalised with unstable angina or non-Q-wave myocardial infarction."

Rhône-Poulenc Rorer acknowledged that these papers were not directly referring to a particular country. The company had spoken with a consultant cardiologist with a special interest in this area who had just conducted and was in the process of writing up a national survey of the treatment of unstable angina in the UK. This survey was funded by the NHS and covered a wide range of practice within the country and showed without doubt that the standard treatment for unstable angina included heparin.

RESPONSE

Pharmacia & Upjohn said that the FRISC study was a registration trial conducted in Sweden. Prior to initiation, it was agreed between the company and the regulatory authorities that Fragmin had to be compared with a standard regimen and that the regimen suggested at the time of conducting the trial in Sweden did not include heparin. Pharmacia & Upjohn said that it had clearly explained in the text below the bar chart that the standard regimen included aspirin, beta-blockers, calcium antagonists and nitrates. Furthermore, in the introduction of The Lancet publication, (Wallentin *et al* (1996)) heparin was not dismissed with the authors stating "in the acute phase, intravenous heparin infusion for 5-7 days is at least as effective as aspirin, but the benefits are short-lived

because of reactivation of the disease soon after the infusion is stopped".

Pharmacia & Upjohn said that in addition, regardless of the opinion of individual authors and doctors, heparin was not always used as part of the treatment regimen of unstable angina in the UK.

In the company's view it had presented the complete picture of what comparators were included and what concomitant medication was accepted in the trial.

PANEL RULING

The Panel noted that the FRISC study had been conducted in Sweden where standard therapy for unstable coronary artery disease did not include heparin. The Panel noted however that there were published data to suggest that standard therapy should include heparin and unpublished data to support the fact that specifically in the UK heparin was a standard component of therapy for unstable coronary artery disease.

The Panel noted that text below the bar chart listed the components of "standard medication" as used in the FRISC study. It was, however, a well accepted principle under the Code that misleading text, labelling etc, could not be qualified by small print. In the Panel's view the majority of readers would assume that "standard medication" would include heparin. The fact that it did not meant that readers were presented with a misleading baseline against which to judge the comparative efficacy of Fragmin. A breach of Clause 7.2 was ruled.

2 Double page heading "Fragmin equals the effectiveness of standard heparin...and facilitates convenient, flexible management"

The double page heading was positioned such that "Fragmin equals the effectiveness of standard heparin..." was along the top of page six and "...and facilitates convenient, flexible management" was at the top of page seven. Page six gave a table of death and morbidity results from a comparative study of Fragmin and standard heparin (the FRIC study) while on page seven there was a graph detailing results from the FRISC study. The two lines on the graph were labelled "standard medication" and "Fragmin + standard medication". Small text below the graph stated "Concomitant medication used in this trial: aspirin, betablockers, calcium antagonists, nitrates".

COMPLAINT

Rhône-Poulenc Rorer considered that the layout of the heading on pages six and seven implied that the data contained on these two facing pages of the detail aid was a comparison with heparin. This was not the case. Data on page six were from the FRIC study, comparing Fragmin and heparin, but the graph on page seven was adapted from the FRISC study which compared Fragmin with placebo. Rhône-Poulenc Rorer said that this representation of the information was misleading in breach of Clauses 7.2 and 7.6.

RESPONSE

Pharmacia & Upjohn said that page six of the detail aid addressed the effectiveness of Fragmin in comparison with heparin which was the main objective of the so-called FRIC Study. This had been presented in the table and the text where incidence figures and p values clearlv stated that there was no difference between the two treatments, Fragmin or standard heparin. Pharmacia & Upjohn considered that the heading "Fragmin equals the effectiveness of standard heparin" was an appropriate heading to the data on the page.

Pharmacia & Upjohn said that the heading on page seven "...and facilitates convenient, flexible management" simply stated the clear benefits of being able to administer Fragmin subcutaneously. Pharmacia & Upjohn did not see how the data on death and morbidity should refer to heparin since the company clearly stated that the two regimens were Fragmin plus standard medication (and the definition of this standard medication was also included under the table) versus standard medication.

Pharmacia & Upjohn could not see any misrepresentation nor could it see any bias in the presentation of the data.

PANEL RULING

In the Panel's view the layout of the two headings "Fragmin equals the effectiveness of standard heparin ..." and "... and facilities convenient flexible management" invited readers to view them as a single sentence. The two headings were visually linked by continuity dots. The Panel considered that the two headings were in fact one heading spanning two pages. The impression given by the heading was that the data given on pages six and seven all compared Fragmin with standard heparin.

The Panel noted that the heading on page six "Fragmin equals the effectiveness of standard heparin ..." was referenced to the FRIC (Fragmin in unstable coronary artery disease) study which was a comparison of Fragmin with standard heparin. The graph on page seven, below the heading ".... and facilities convenient flexible management", was, however, from the FRISC study which had compared Fragmin with "standard medication". The explanation of "standard medication" was in small print below the graph and did not include heparin. The Panel considered that given the headline most readers would assume that "standard medication" had included standard heparin which was not so. The fact that this had been explained in the small print was not acceptable under the Code. The Panel considered that the headline together with the presentation of the FRISC data was misleading in breach of Clause 7.2 of the Code.

The Panel considered that its ruling of a breach of Clause 7.2 covered the allegation of a breach of Clause 7.6 and made no ruling in this regard.

3 Table comparing the efficacy of a low molecular weight heparin (LMWH) versus standard heparin

Near the bottom of page seven was a subheading "Efficacy of LMWH confirmed in 3,000-patient study" underneath which was a table of results showing an advantage for "LMWH" in terms of a combined endpoint of death, MI and recurrent angina, compared to "standard

heparin". Below the table in small print it was stated that the study had used the low molecular weight heparin enoxaparin (Rhône-Poulenc Rorer's product Clexane).

COMPLAINT

Rhône-Poulenc Rorer said that the table on page seven which compared LMWH with heparin was a reproduction of data from the ESSENCE study which compared enoxaparin and heparin. Rhône-Poulenc Rorer considered that the presentation of the data in this format misled the reader into believing that the data referred to Fragmin. The company submitted that different low molecular weight heparins had different molecular weight distributions, bioavailability, plasma clearances, half lives and, importantly, different anti-thrombotic activity. Rhône-Poulenc Rorer considered that it was inappropriate to use data from an enoxaparin study in this manner to support dalteparin. Breaches of Clauses 7.2 and 7.6 were alleged.

RESPONSE

Pharmacia & Upjohn said that it understood the complaint to be that the subheading "Efficacy of LMWH confirmed in 3,000-patient study" would be taken to refer to Fragmin. The company could not see how this could be interpreted in such a way as Fragmin was not used in the text or the table and the only study referred to was the ESSENCE study. With regard to the comment on whether end points could be discussed as a class effect the company agreed that different LMWHs had different pharmacological and pharmacokinetic properties. However, there were no published data to date which unequivocally confirmed that these differences could be translated into clinical differences. In summary Pharmacia & Upjohn said it had simply presented data from the well known ESSENCE study.

PANEL RULING

The Panel noted that the sub-heading "Efficacy of LMWH confirmed in 3,000 patient study" and the table of results related to the ESSENCE study which was a comparison of enoxaparin and standard heparin. There was no mention of ESSENCE but details of the comparators were given in small print below the table. The Panel noted, however, that it was a well accepted principle under the Code that misleading headlines, text etc could not be qualified by small print. In the Panel's view the majority of readers would assume that the LMWH question and the results all related to Fragmin as the information had been given in a Fragmin detail aid. The Panel noted that there were pharmacological and pharmacokinetic differences between the various low molecular weight heparins and so considered that the specific data from the ESSENCE might not be applicable to any other product than enoxaparin.

The Panel considered that the ESSENCE study data had been presented in such a way that readers would assume that it referred to Fragmin which was not so. The Panel considered that the presentation of the data was misleading in breach of Clause 7.2.

The Panel considered that its ruling of a breach of Clause 7.2 covered the allegation of a breach of Clause 7.6 and made no ruling in this regard.

4 Promotion of an unlicensed indication

COMPLAINT

Rhône-Poulenc Rorer said that use of the data from the ESSENCE study, in which patients with unstable coronary artery disease were given enoxaparin, represented the promotion of an unlicensed indication for enoxaparin in breach of Clause 3.2 of the Code.

RESPONSE

Pharmacia & Upjohn drew attention to the definition of promotion (Clause 1.2) which was that the term "promotion" meant any activity undertaken by a pharmaceutical company or with its authority which promoted the prescription, supply, sale or administration of its medicines.

Pharmacia & Upjohn submitted that as enoxaparin was not one of its products the inclusion of the ESSENCE data would not fall into the scope of the Code as the company was not promoting enoxaparin.

PANEL RULING

The Panel did not consider that the presentation of the ESSENCE data represented promotion of enoxaparin for an unlicensed indication. Enoxaparin was not Pharmacia & Upjohn's product. No breach of Clause 3.2 was ruled.

Complaint received **19 September 1997**

Case completed **8 December 1997**

CASE AUTH/615/9/97

NO BREACH OF THE CODE

GENERAL PRACTITIONER v SOLVAY

Newspaper article on Physiotens

A general practitioner complained about an article headed "Exciting new drug stops the pulse racing" which had appeared in The Times and which referred to Physiotens, one of Solvay's products. He had been unhappy to have it presented to him by one of his patients and considered that it read like a promotional review. He accepted that Solvay was not directly behind it but considered that there should be some mechanism for preventing this sort of article.

The Panel noted that Solvay had not been consulted on the article. The author had been provided with an abstract of clinical data on Physiotens presented at a meeting. The author had visited Solvay's facilities in Hanover and Neustadt. The Panel noted that articles in the press were judged on the information provided by the company rather than on what the articles said. The Panel considered that the information provided was reasonable and did not constitute an advertisement and ruled that the Code had not been breached.

A general practitioner complained about an article headed "Exciting new drug stops the pulse racing" which appeared in The Times, 28 August 1997. The article had been written by Dr Thomas Stuttaford, the medical columnist of The Times. The article referred to the arrival of a new medicine, Physiotens (one of Solvay Healthcare Ltd's products), and to clinical data presented at the European Society of Cardiology earlier that week.

COMPLAINT

The complainant stated that he was unhappy to be presented with the article by one of his patients. He considered that the article read like a highly promotional review. The complainant accepted that Solvay would not have been directly behind the article but considered that there should be some mechanism for preventing this sort of article which the complainant did not believe had been placed in a proper context.

Solvay was asked to consider the requirements of Clauses 20.1 and 20.2 of the Code.

RESPONSE

Solvay stated that the article was written without any reference or input from Solvay. The views expressed were those of an eminent practising physician who was also a medical media commentator. Solvay was not consulted in any way on the content of the article.

With regard to contacts with The Times, Solvay explained that its German company regularly invited journalists to visit its facilities. Dr Stuttaford visited the research and development centre in Hanover and the production site in Neustadt in August 1997. During the visits discussions were held on the whole drug development process from computerised molecular modelling techniques for the synthesis of possible target compounds through screening of compounds using non-animal robotised techniques, on new production methods for pancreatic enzymes and on medicines in research and development including Physiotens. Dr Stuttaford was also given a tour of the new pharmacology building.

Solvay stated that it had provided Dr Stuttaford with an abstract of clinical data on Physiotens which were presented at the European Society of Cardiology meeting held in Stockholm on 27 August. Dr Stuttaford had already received several invitations to attend the meeting.

Solvay pointed out that Physiotens was launched in the UK in September 1996. It had been included in reference books such as the British National Formulary and MIMS since that time. A copy of the press release relating to the launch of the product was provided together with a list of recipients. There had been no other press releases/packs dealing with the product.

Solvay submitted that it had not contravened the Code in any way. The specific clauses mentioned by the Authority, Clauses 20.1 and 20.2, related to the prohibition of advertising to the general public and the factual accuracy and balance of information made available to the general public. Solvay submitted that it had provided accurate information relating to Physiotens and the article in question was entirely the responsibility of the author.

Solvay had informed Dr Stuttaford about the complaint and he was rather offended that anyone would suggest that he had written the article as part of a promotional campaign. He also considered that the Authority should be told that he took the opportunity of his visit to Hanover to discuss Physiotens as he knew one of the first patients in the country to be treated with the product. This was one of the reasons why he accepted the invitation.

PANEL RULING

The Panel noted Solvay's submission that it was not consulted in any way on the content of the article in question. The author had been provided with an abstract of clinical data on Physiotens, presented at the European Society of Cardiology meeting held in Stockholm. According to the company's submission, the press launch materials had not been sent to the lay media. They had been sent to the medical and pharmaceutical press in September 1996. The author had been to visit Solvay's facilities in Hanover and Neustadt in August 1997. The Panel did not know what had been said about Physiotens during that visit.

The Panel noted that complaints about articles in the press were judged on the information provided by the pharmaceutical company or its agent to the journalist and not on the content of the article itself. It was not necessarily a breach of the Code to include brand names in materials for the press.

The Panel considered that the information supplied by Solvay, namely the clinical data presented at the

European Society of Cardiology meeting, was not unacceptable. The Panel did not accept that the information provided by Solvay constituted an advertisement and no breach of Clause 20.1 of the Code was ruled.

The Panel noted the requirements of Clause 20.2 of the Code that information about a medicine made available to the general public either directly or indirectly must be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. The Panel considered that the information provided to the author was reasonable and therefore ruled no breach of Clause 20.2 of the Code.

Complaint received 25 September 1997

Case completed 12 November 1997

CASE AUTH/616/9/97

CONTINENCE ADVISOR v LOREX SYNTHÉLABO

Video "Bladders Behaving Badly"

A continence advisor complained about a video entitled "Bladders Behaving Badly" which was sponsored by Lorex Synthélabo alleging that a statement made in it about the use of a nasal spray, presumably desmopressin (Desmospray), that it "...stops you passing water of any description for 24 hours" was inaccurate information and might confuse both professional staff and patients who viewed the video.

The Panel noted that the statement at issue was not medically precise and represented either an error or the patient's genuine but mistaken belief about the nasal spray's clinical effect. The patient suffered from stress incontinence which was not a licensed indication for Desmospray. The material was not factual and was misleading as to the treatment options which might be available to those with severe urinary stress incontinence. A breach of the Code was ruled.

A continence advisor at an NHS Trust complained about a video entitled "Bladders Behaving Badly" which was sponsored by Lorex Synthélabo Ltd. The video was intended for patients. It contained profiles of three patients who suffered from urinary incontinence and culminated in a studio discussion between these patients and a presenter about the effect that the condition and its treatment had upon their lives. During this discussion a patient stated that a nasal spray "... stops you passing water of any description for 24 hours".

COMPLAINT

The continence advisor alleged that the video gave inaccurate information about a particular treatment option. The complainant had written to Lorex Synthélabo about the video to express concern at a statement made by one of the patients that the use of a nasal spray, presumably desmopressin, "... stops you passing water of any description for 24 hours". The complainant was concerned that this inaccurate information might confuse both professional staff and patients who viewed the video.

RESPONSE

Lorex Synthélabo stated that the video was intended to be given by continence advisers to patients to be viewed at home or for a continence adviser to show to groups of patients. As such, Lorex Synthélabo thought it was important to make it a realistic video using actual patients that fellow sufferers could identify with and be reassured that urinary incontinence was a common problem experienced by people like themselves and that effective help was at hand and they should not be afraid to come forward.

It was for this reason that the video was made using real patients who were unscripted. Lorex Synthélabo wanted to present the patients speaking about their own problems in their own words. Lorex Synthélabo stated that the video was not in any way a promotional item.

Lorex Synthélabo stated that in any unscripted production using real patients talking about medical matters, one always ran the risk that they might have acquired incorrect information from whatever source and that some misconceptions that they held about their condition or its treatment might appear.

Lorex Synthélabo conceded that the statement made in the video by the patient that the nasal spray (presumably Desmospray (desmopressin), although this was not said) "... stops you passing water of any description for 24 hours" was not medically precise, but submitted that one had to look at the context in which the statement was made.

Lorex Synthélabo pointed out that the section in which the statement was made occurred at the end of the video, and consisted of an open discussion between the presenter and the three patients who had appeared earlier in the video. This discussion was filmed live in a television studio. The only scripting that was used was that of the introduction and conclusion by the presenter. The rest was a spontaneous discussion unscripted and appeared in the video exactly as it happened, with no editing.

Lorex Synthélabo submitted that under those circumstances, either the patient was saying what she actually believed to be true and what her experience with the 'nasal spray' was, or in the setting of a television studio with a celebrity presenter interviewing her, she made a mistake in referring to the effect the product had on her.

Lorex Synthélabo stated that patients were not doctors. If one wanted the impact and realism of using actual

patients one would have to expect that the occasional medical inaccuracy might occur. Just listening to any radio or television broadcast on medical topics where real patients were interviewed showed that often patients had misconceptions about their illness or its treatment, but no suggestion was made that broadcasts on medical matters should not go out if the words a patient used were not 100% medically correct.

Lorex Synthélabo stated that the vast majority of professional staff viewing the video would be continence advisers who would look at the video when it was given to them and would also view it if they showed it to groups of patients. Continence advisers were a very specialised and knowledgeable group of nurses who were fully aware of the medical treatment options in urinary incontinence. Lorex Synthélabo submitted that there was no possibility whatsoever that these expert practitioners would be confused by what the patient had said in the interview into believing that Desmospray stopped all urine production for 24 hours. They would in fact, see it for what it was - a minor error of medical fact made by a lay person.

Lorex Synthélabo stated that from the point of view of patients seeing the video one must not only ask would it confuse, but go on to consider the more important issue that if it did confuse, was this confusion likely to have a detrimental effect on patients viewing the video such that the risk of them being confused about the mode and duration of action of Desmospray outweighed the benefit they would achieve by viewing the rest of the video.

Lorex Synthélabo reiterated that the aim of this video was to reassure patients that urinary incontinence was a common problem experienced by people just like themselves; that effective help was available and they should not hesitate to come forward. Looking at it this way, Lorex Synthélabo believed that it was highly unlikely that this slight factual error spoken by one of the patient participants in the video would deter patients from coming forward for help.

In fact, submitted Lorex Synthélabo quite the opposite might happen. The patient in the video suffered with severe urinary incontinence and said that she normally took tablets for this which helped control the situation. But when she really needed to be sure of being dry for long periods of time, in a board presentation for example, she used the nasal spray which she described as a 'safety net' for her.

Lorex Synthélabo submitted that this could act to reassure patients with severe incontinence that, no matter how severe their problems were, there were treatment options available which could effectively control their symptoms. Lorex Synthélabo believed that there was little or no risk that patients would be confused by imprecise medical information in the video, and any risk of this happening was far outweighed by the overall benefit that this video (the only one of its kind) would have in reassuring patients with urinary incontinence that they were not alone and that effective help was available for this common yet highly embarrassing condition.

PANEL RULING

The Panel noted that the statement at issue was not medically precise and represented either an error or the patient's genuine but mistaken belief about the nasal spray's clinical effect.

The Panel noted that the patient suffered from stress incontinence, the treatment of which was not a licensed indication for Desmospray. The Panel noted that the data sheet for Desmospray stated that it was indicated for the treatment of primary nocturnal enuresis, nocturia associated with multiple sclerosis where other treatments had failed, the diagnosis and treatment of vasopressin-sensitive cranial diabetes insipidus and establishing renal concentration capacity (ref ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1996-97).

The Panel noted that the statement was not factual. It appeared in material designed for patients and was misleading as to the treatment options which might be available to those with severe urinary stress incontinence. The Panel therefore ruled a breach of Clause 20.2 of the Code.

Complaint received **26 September 1997**

Case completed **20 November 1997**

RESEARCH ETHICS COMMITTEE v GLAXO WELLCOME

Serevent and fluticasone studies

A research ethics committee complained about three studies being undertaken by Glaxo Wellcome, all of which used Glaxo Wellcome's Accuhaler. The committee considered that a single study using the Accuhaler would perhaps have passed without comment but three, so close together, all of which required the use of the Accuhaler, suggested that perhaps the studies might be promoting the use of Accuhalers in the minds of both patients and clinicians.

One of the studies concerned had already been the subject of complaint by the research ethics committee and had been ruled not to be in breach of the Code (Case AUTH/610/8/97).

The Panel noted that the only provision in the Code relating to clinical trials and the like was a requirement that clinical studies must not be disguised promotion. Any study would have some promotional impact but studies must not be such as to be promotion *per se*. Each of the studies complained of required the use of the Accuhaler and the primary issue was whether the studies had a genuine scientific purpose or whether, individually or collectively, they were disguised promotion for the Accuhaler. The Panel noted that one of the studies had been the subject of a previous case and considered that in each of the other two the study had been conducted in an attempt to answer a valid scientific question. The Panel considered that the studies did not constitute disguised promotion of the Accuhaler and ruled that there had been no breach of the Code.

A research ethics committee complained about three studies undertaken by Glaxo Wellcome UK Limited. One of the studies had been the subject of an earlier complaint from the same research ethics committee (Case AUTH/610/8/97). The Panel had ruled no breach of the Code and the research ethics committee had not appealed that decision.

COMPLAINT

A director of public health complained on behalf of a research ethics committee which had identified a number of issues in each study. Its main concern was that all the studies used the multi-dose powder inhaler Accuhaler, produced by Glaxo Wellcome. The research required patients to change from their existing inhalers to the Accuhaler, when perhaps traditional preparations not requiring a change existed, thus creating possible difficulties for patients associated with such a change. The research ethics committee considered that a single study which required this would perhaps have passed without comment. However, three, so close together, which all required the use of the Accuhaler, suggested that perhaps these studies might be promoting the use of Accuhalers in the minds of both patients and clinicians. The studies which gave rise to concern were:

SLGB 4020 A phase IV, multi-centre, double-blind, randomised, parallel group study to investigate whether the addition of salmeterol (Serevent) 50mcg bd or 100mcg bd shortened recovery time and hence in-patient time for patients hospitalised with asthma. This study had been the subject of the earlier complaint referred to above.

SLGB 4021 A study of the effect of Serevent on the daily physical activity and quality of life of asthmatic children.

FLTB 3049 A phase III, randomised, double-blind, parallel group study to compare the efficacy of inhaled fluticasone 100mcg given once daily and fluticasone 50mcg given twice daily, both delivered via the multi-dose powder inhaler, in children aged 4-16 years with mild to moderate, stable asthma.

RESPONSE

Glaxo Wellcome pointed out that study SLGB 4020 had recently been considered by the Panel which had ruled that there had been no breach of either Clause 10.2 or Clause 18.

Glaxo Wellcome addressed the further two studies in turn.

1 A multi-centre, double-blind, parallel group, placebo controlled study to assess the effect of Serevent (salmeterol xinafoate) 50mcg bd via the Accuhaler, on the daily physical activities of asthmatic children and their quality of life. Protocol No. SLGB 4021.

Glaxo Wellcome stated that this study was designed in response to requests from respiratory paediatricians throughout the UK who wished to see the results of a well-designed study examining the benefits for children of using inhaled salmeterol (Serevent), in as near to a real-life situation as could be obtained in a clinical trial.

Hence, the study's objectives were:

a) To assess the effect of treatment with Serevent 50mcg bd on the daily physical activities of children and their quality of life, and

b) To determine if regular use of Serevent could protect against the symptoms of asthma induced by daily physical activities, without the need for additional short-acting β_2-agonists.

Glaxo Wellcome stated that children aged 8-11 years, with symptomatic asthma, receiving inhaled corticosteroid therapy or sodium cromoglycate would be eligible. Their pre-existing prophylactic therapy would be continued with no change either to the type of agent taken or its delivery device. However, both the Serevent and matching placebo, and Ventolin (salbutamol) would be provided as study medication, taken via the Accuhaler device. Glaxo Wellcome submitted that the Accuhaler was a device particularly suitable for children, it contained 60 doses, was convenient to carry, had a doses-remaining counter and was easy to operate reliably and consistently. Apart from being clinically appropriate, it was valuable in this study as the dosage counter helped to confirm the number of doses of medication which had been taken, which was one of the outcome variables for this study (prn short-acting β_2-agonist, ie Ventolin), as well as

assisting in compliance monitoring for the Serevent/placebo.

Glaxo Wellcome provided the Panel with a protocol amendment which was made when it was appreciated that there had been an over estimation of the number of patients required for each group. The study required 66 patients with evaluable data rather than 112, but the number dropping out would need to be monitored closely to ensure that sufficient patients completed the study. Patients were being recruited in 30 centres throughout the UK. Approval had already been received after minor changes to the patient information from one of the newly established multi-centre research ethics committees.

Glaxo Wellcome stated that the investigator payment for the study was £500 for each patient completing the study, based on the British Medical Association suggested rates of £126/hour. It believed that this represented a fair reflection of the amount of work involved and was not in breach of Clause 18.1 of the Code.

It did not believe that this scientifically designed study could be viewed as being promotional for the Accuhaler and was therefore not in breach of Clause 10.2 of the Code.

2 A phase III, randomised, double-blind, parallel group study to compare the efficacy of inhaled fluticasone propionate 100mcg given once daily and fluticasone propionate 50mcg given twice daily, both delivered via the multi-dose powder inhaler in children aged 4-16 ears with mild-to-moderate stable asthma. Protocol No. FLTB 3049.

Glaxo Wellcome stated that this study had been designed to compare the efficacy of once daily and twice daily inhaled fluticasone therapy in children with stable asthma. The ability to recommend once daily therapy for stable asthma might assist compliance with prescribed therapy and might be a useful stage in the "stepping down" of inhaled corticosteroid therapy to the lowest effective level. This approach was referred to in the British Guidelines on Asthma Management and the North of England Evidence Based Primary Care Asthma Guidelines. Understandably, there was an ever increasing emphasis upon supporting prescribing recommendations with evidence from well designed studies ie randomised controlled trials, such as the one which was the subject of this complaint.

Glaxo Wellcome stated that it would be necessary to have evaluable data from 308 patients in order to demonstrate equivalence between the two study medications with 90% power. Initially it was considered that 362 patients from 100 centres would be necessary to achieve this result, but this had been revised to 420. To date, 93 centres had been set up throughout the UK following approval by their local research ethics committees.

Glaxo Wellcome submitted that the multi-dose powder inhaler (Accuhaler) was appropriate for this group of patients. It was convenient, reliable and popular with children. As the use of short-acting β_2-agonist (Ventolin) was one of the outcome measures for this study, the availability of a dosage counter was invaluable. This study involved fluticasone in the Accuhaler device. It had been set up to answer a question concerning once or twice daily inhaled fluticasone (introduced in 1993), which was most reliably delivered in this age group by the Accuhaler device (introduced in 1995).

Glaxo Wellcome stated that it was a coincidence that the development of these studies had led to them being submitted to the local research ethics committee within months of one another. The promotion of the Accuhaler was not carried out through the medium of complex scientific studies.

This study involved 5 patient visits to the participating doctor and the fee was £450 for each patient who completed the study or as set out in the letter of agreement (a copy of which was enclosed). Glaxo Wellcome submitted that this was a scientific study, set up to answer a valid question and it was not in breach of Clause 10.2 of the Code. The investigator fees were in line with the BMA recommended scale and it believed that the study was not in breach of Clause 18.1 of the Code.

PANEL RULING

The Panel noted that study SLGB 4020 had been the subject of Case AUTH/610/8/97 when it had ruled no breach of Clause 10.2 or Clause 18 of the Code.

The Panel noted that the only clause in the Code relating to clinical trials and the like was Clause 10.2 which required that clinical studies must not be disguised promotion. The Panel accepted that any study would inevitably have some promotional impact but studies must not be such that they were promotional *per se*. Each study required the use of the Accuhaler. The primary issue was whether the studies had a genuine scientific purpose or whether individually or collectively they were disguised promotion for the Accuhaler.

Firstly, the Panel considered study SLGB 4021. The Panel noted that the introduction to the protocol stated that Serevent at doses of 50, 100 and 200mcg had been shown to have a bronchodilator effect of twelve hours. The rationale for the study referred to previous studies assessing the use of salmeterol in exercise induced asthma which had generally been single dose, laboratory-based studies. The rationale stated that such studies did not reflect real-life and did not take into account spontaneous physical activity. The short duration of action of beta$_2$-agonists such as salbutamol relied upon children taking treatment at school prior to physical activities. The objectives of the study were to assess the effect of treatment with Serevent 50mcg bd on the daily physical activities of children and their quality of life and to determine if regular use of Serevent could protect against symptoms of asthma induced by daily physical activities without the need for additional short-acting beta$_2$-agonists.

The Panel noted that patients should continue with their asthma medication as usual. All blinded medication was supplied by Glaxo Wellcome in Accuhaler devices. In addition Ventolin Accuhaler would also be provided as relief medication for use during the study. The Panel accepted Glaxo Wellcome's submission that the use of the Accuhaler with its dosage counter to help confirm the number of doses taken, which was one of the outcome variables for the study, would be valuable and would also assist with patient compliance.

The Panel considered that the study was being conducted in an attempt to answer a valid scientific question. The Panel did not consider that the study constituted disguised promotion and ruled no breach of Clause 10.2 of the Code.

The Panel noted that the study involved 5 visits to the investigator over a 12 week period and considered that the investigator payment of £500 was reasonable given that the BMA suggested fee for participation in a clinical trial was £126 per hour. No breach of Clause 18.1 of the Code was ruled with regard to the payments for the study.

Secondly the Panel considered study FLTB 3049. The Panel noted that the objective of study FLTB 3049 was to compare the efficacy of fluticasone propionate 100mcg given once daily and 50mcg fluticasone twice daily in children with mild-to-moderate, stable asthma. The study would assess 420 patients in approximately 100 centres and was a double blind, parallel, group study.

Patients receiving or requiring 100mcg fluticasone or 200mcg beclomethasone or budesonide daily for the prophylaxis of asthma were eligible for inclusion in the study. Patients in the study could not use inhaled corticosteroids for asthma other than study medication, short acting bronchodilators other than study relief medication, oral or systemic corticosteroids, sodium cromoglycate or theophylline. Patients requiring new asthma medications during the study had to be withdrawn. Regulatory approval had to be obtained.

The Panel noted that the study medication, fluticasone and placebo was provided by Glaxo Wellcome in Accuhaler devices. Salbutamol Accuhaler was also provided.

The Panel accepted Glaxo Wellcome's submission regarding the reasons for using the Accuhaler device in this study. These were similar to the reasons given for study SLGB 4021.

The Panel considered that the study was being conducted in an attempt to answer a valid scientific question. The Panel did not consider that the study constituted disguised promotion and ruled no breach of Clause 10.2 of the Code.

The Panel noted that the study involved 5 patient visits to the investigator over an eight week period and considered that the investigator fee of £450 was reasonable given the BMA suggested fee of £126 per hour. No breach of Clause 18.1 of the Code was ruled with regard to the payments for the study.

The Panel accepted that a well designed study would inevitably have some promotional impact and hence an effect of these studies, individually or collectively, might be to increase the use of the Accuhaler. The Panel considered however that collectively the studies did not constitute disguised promotion of the Accuhaler. No breach of Clause 10.2 of the Code was ruled.

Complaint received **6 October 1997**

Case completed **23 December 1997**

CASES AUTH/619/10/97 AND AUTH/622/10/97

GENERAL PRACTITIONERS v WYETH

Zoton calendar

Two general practitioners complained about a Zoton calendar issued by Wyeth. One alleged that the cartoons which it contained were in extremely bad taste and considered them to be of a lower standard than would be permitted in the tabloid press. They displayed vulnerable patients in humiliating and degrading circumstances and invited the viewer to collude in finding it funny. The other complainant said that the images were demeaning and could well cause offence. The calendar was unacceptable.

The Panel accepted that issues of humour and taste were subjective matters but concluded that the cartoons, which were demeaning to patients, were likely to cause offence. The company had failed to maintain a high standard and a breach of the Code was ruled.

Two general practitioners complained about a Zoton Calendar issued by Wyeth (ZOT742/0797).

The calendar ran from September 1997 to December 1998. For each month there was a cartoon. Almost all of the cartoons featured patients lying on a table having, or about to have, an endoscopy.

Case AUTH/619/10/97

COMPLAINT

A general practitioner, who had received the calendar by post, said that he thought that all the cartoons, but particularly those for April and July, were in extremely bad taste. He could not understand why the company produced and distributed them since he could not imagine where in a hospital, surgery or home they could be displayed without causing offence and distress to anybody viewing them.

The complainant alleged a breach of Clause 9.1 of the Code as the cartoons were likely to cause offence to members of the healthcare professions. They displayed vulnerable patients in humiliating and degrading circumstances and invited the viewer to collude in finding it funny. The cartoons were of a much lower standard and taste than would be permitted in the tabloid press and the complainant hoped that they would not be publishable in any medical journal or newspaper. The display of naked and partially naked cartoon people for no justifiable clinical or aesthetic purpose was another factor.

The complainant referred to Clause 14 which required that the promotional material should have been certified on behalf of the company by a doctor. Assuming that this

procedure was followed, the complainant wondered how the doctor reconciled that decision with his professional duty to make the care of one's patient the first concern, respect the patient's dignity and privacy and avoid bringing the medical profession into disrepute and to uphold good standards of ethics and practice.

Case AUTH/622/10/97

COMPLAINT

A general practitioner, who had been given a copy of the calendar following a visit by a pharmaceutical company representative, said that he considered that the images portrayed were demeaning and could well cause offence. They were particularly likely to cause offence to patients should the calendar be found in, for example, a doctor's consulting room. The complainant alleged that the calendar was unacceptable and said that the company should withdraw it.

Cases AUTH/619/10/97 & AUTH/622/10/97

RESPONSE

Wyeth was surprised and concerned to receive the two complaints about the calendar. The calendar was intended to be light hearted medical humour. The use of exaggerated cartoon characters was intended to emphasise the humour and to depersonalize the illustrations thus avoiding any offence. Distribution was limited to doctors and there were no plans to use the cartoons more widely.

The company appreciated that good or bad taste and humour were matters of personal opinion which might not be shared by others. It was never the company's intention to cause offence. The company therefore made the decision to cease distribution of the calendar immediately.

PANEL RULING

The Panel examined the cartoons used in the calendar in relation to the requirements of Clause 9.1 of the Code that materials and activities must recognise the special nature of medicines and the professional standing of the audience and must not be likely to cause offence. High standards must be maintained at all times.

The Panel accepted that issues of humour and taste were a subjective matter but considered that the cartoons, which were demeaning to patients, were likely to cause offence. The company had failed to maintain a high standard. The Panel therefore ruled a breach of Clause 9.1 of the Code.

Complaints received

Case AUTH/619/10/97	**9 October 1997**
Case AUTH/622/10/97	**13 October 1997**
Cases completed	**18 November 1997**

CASE AUTH/620/10/97

PHARMACEUTICAL ADVISOR v GLAXO WELLCOME

Regional Therapeutic News

The principal pharmaceutical advisor to a health authority complained about Regional Therapeutic News No. 28 which was entitled "Inhaled Steroids". The complainant said that the glossy publication appeared to have been specifically designed to deceive prescribers into believing that it had been printed by an official NHS source, such as a regional NHS executive office or a regional drug information unit. It was only when one read all the way through it that one came across prescribing information for Flixotide and a statement that it had been supported by an educational grant from Allen & Hanburys Ltd.

The Panel considered that the appearance of the publication, in particular its title and the inclusion of an editorial by a local consultant on the front page, gave the impression that it had been independently produced. The article in the publication, "Inhaled corticosteroids: current issues and clinical experiences", showed fluticasone in a favourable light, almost a half page text being devoted to clinical studies with it. No other corticosteroid was similarly mentioned. The Panel noted that Glaxo Wellcome accepted that the publication was promotional in nature. The Panel did not consider that the sponsorship had been made sufficiently clear and considered that the publication looked as if it had been produced independently and ruled it in breach in both these respects.

The principal pharmaceutical advisor to a health authority complained about an issue of Regional Therapeutic News, No. 28 - September 1997, sent to general practitioners by Allen & Hanburys Ltd. The six page, A4, folded publication was entitled 'Inhaled Steroids' and on the front cover there was an editorial written by a consultant paediatrician. The front cover also explained that the aim of Regional Therapeutic News was to bring readers the views of both national and local opinion leaders. The title of the article in it was "Inhaled corticosteroids: current issues and clinical experiences". There were a number of general headings throughout the article with one half page of text describing "Fluticasone propionate: clinical studies". The article contained four figures, one showed the order of uptake and retention of inhaled corticosteroids in human lung tissue, two detailed results of a meta-analysis of studies comparing fluticasone and budesonide and a fourth gave results of a study comparing fluticasone and sodium cromoglycate in asthmatic children. The article had been written by a consultant physician. Page six of the publication carried the prescribing information for Flixotide Accuhaler, Diskhaler and Inhaler. Beneath the prescribing information was a statement in bold "Supported by an educational grant from Allen & Hanburys Ltd". The colour used throughout the publication, apart from black and white, was orange.

The publication had been distributed in envelopes which bore, in the top left hand corner, the boxed Regional Therapeutic News logo underneath which was printed "Bringing you the views of your local consultants". On the back of the envelope was the name and address of the publishers.

COMPLAINT

The complainant said that the glossy publication appeared to be have been specifically designed in order to attempt to deceive prescribers into believing it had been printed by an official NHS source, such as a regional NHS Executive office, or regional drug information unit. The attempt to deceive was further compounded by the issue stating "No. 28 - September 1997" on the front cover, leading prescribers to think that this was a long-standing and well-established official publication. It was only when one read all the way through the publication that one noticed 'Abridged Prescribing Information' for Flixotide products, and a line stating "Supported by an educational grant from Allen & Hanburys Ltd".

The complainant said that it was her opinion, and that of the medical advisor of the health authority, that this was cynically designed to attempt to deceive, and that this therefore breached Clause 10 of the Code.

RESPONSE

Glaxo Wellcome UK Limited pointed out that as stated on its back page, Regional Therapeutic News was published in the UK by a medical publisher. The complainant was presumably unaware that it was first published in July 1994 and this was indeed its 28th issue. Previous issues had covered a multitude of topics and had been sponsored by a wide spectrum of pharmaceutical companies. The format had remained unchanged over the past three years with a front page which carried an introduction by a relevant regional/local specialist whose name, position and working address were all prominently shown at the foot of the foreword. The wording below the title, in this case "Inhaled corticosteroids", had remained the same with no suggestion that this item had come from the Regional Office of the NHSE.

Glaxo Wellcome said that issue No. 28 of Regional Therapeutic News had on the front page the orange colour associated with Flixotide (fluticasone propionate), while on its back page was the prescribing information for Flixotide, together with a statement "Supported by an educational grant from Allen & Hanburys Ltd".

Glaxo Wellcome said that the original envelopes had the "Regional Therapeutic News" box coloured orange. Below that there was a clear statement "Bringing you views of your local consultants" and the name and address of the publisher was on the flap. Glaxo Wellcome said that it had always viewed this issue of Regional Therapeutic News as being of a promotional nature and the company did not believe that it was in breach of either Clause 9.9 or 10.1 of the Code of Practice, as sponsorship was clearly stated and there had been no attempt to disguise its promotional nature.

Glaxo Wellcome said that the issue of Regional Therapeutic News which was the subject of this complaint was one of a series of five which was distributed to

general practitioners, by post, on a regional basis. The article reflected the proceedings of a round table meeting held in October 1996. The programme included a number of discussions about issues surrounding the use of inhaled corticosteroids, details were provided.

A draft report of the round table meeting was written by a scientific writer and was then amended by a consultant respiratory physician who was one of the contributors to the meeting for publication in Regional Therapeutic News. Glaxo Wellcome said that its involvement was through its normal approvals process for promotional items following which it was finally reviewed by the consultant physician.

Glaxo Wellcome said that a series of regional round tables was held in the first half of 1997 and these were chaired by the writers of the forewords to the regional issues. Again, these went through Glaxo Wellcome's normal approvals process and underwent only minor textual amendments before final review by their authors. Details of the five regional issues were provided.

PANEL RULING

The Panel examined the Regional Therapeutic News in question and considered that its appearance gave the impression that it had been independently produced. Its title, "Regional Therapeutic News" and the inclusion of an editorial on the front page from a local consultant suggested that it might have been locally produced. The Panel did not accept that readers would automatically associate the orange colour of the publication with Flixotide.

The article printed in the publication was entitled "Inhaled corticosteroids: current issues and clinical experiences". Much of the text was of a general nature but where examples had been given to illustrate various points the corticosteroid mentioned was usually fluticasone, often being favourably compared with another product. Figures of results all showed fluticasone in a favourable light. Almost one half page of text was devoted to clinical studies with fluticasone. No other corticosteroid was similarly mentioned.

The Panel noted that Glaxo Wellcome accepted that the publication was promotional in nature. Prescribing information for Flixotide was included on the back page as was the statement "Supported by an educational grant from Allen & Hanburys Ltd". The Panel did not consider however that the sponsorship of the publication was made sufficiently clear to those reading it. It looked as if it had been produced independently. In the Panel's view the publication was disguised promotion for Flixotide and so a breach of Clause 10.1 was ruled.

The Panel noted that the supplementary information to Clause 10.1 of the Code referred to the need for companies to declare sponsorship on company sponsored material as required by Clause 9.9 of the Code. The Panel considered that the declaration of sponsorship on the Regional Therapeutic News was not sufficiently clear and accordingly ruled a breach of Clause 9.9 of the Code.

The Panel noted that the 1998 edition of the Code would include supplementary information to Clause 9.9 stating that "The declaration of sponsorship must be sufficiently prominent to ensure that readers of sponsored material are aware of it at the outset".

During its consideration of this case the Panel noted that the envelope used to distribute the Regional Therapeutic News gave no indication of the promotional nature of its contents. The envelope carried the Regional Therapeutic News logo on the front and the name and address of the publishers of the publication on the back. The envelope gave the impression that it contained locally produced "official" material. The Panel noted Glaxo Wellcome's submission that the Regional Therapeutic News logo was boxed in orange but did not accept that this would give any indication as to the promotional nature of the envelope's contents. The Panel noted the supplementary information to Clause 10.1 that envelopes must not be used for the dispatch of promotional material if they bear words implying the contents were non promotional. The Panel considered that the envelope was unacceptable as it amounted to disguised promotion and requested that Glaxo Wellcome be advised of its views.

Complaint received **9 October 1997**

Case completed **4 December 1997**

CASES AUTH/623/10/97 and AUTH/638/11/97

HOSPITAL PHARMACIST v NOVEX PHARMA AND ALLERGAN

Conduct of representative

The pharmacy manager at a hospital complained about the conduct of a representative from Novex Pharma who had been promoting Zorac Gel, an Allergan product. The representative had not spoken to the pharmacy or left any information before promoting the product, contrary to hospital policy. The representative had arrived at the pharmacy with an outpatient who had a prescription for Zorac Gel. The complainant had asked the patient and the representative to take a seat whilst she spoke to the prescriber. When she called the patient to explain about obtaining the product, the representative stood up and approached the counter. The complainant considered it unacceptable that a representative had brought a prescription for a new product to the pharmacy.

The Panel considered that Allergan was responsible for the conduct of the contract representative as far as the Code was concerned as it was an Allergan product that was being promoted. Novex Pharma was acting as a contract representative company to promote Zorac Gel on behalf of Allergan. Novex Pharma could not therefore be in breach.

The Panel noted that the representative had talked to the patient in the waiting room while waiting to see the consultant dermatologist. The patient was called in to see the consultant. The representative had been invited to join them. In the Panel's view, the representative must have given the patient the impression that she had a product for psoriasis for this to have happened. The Panel considered that the representative, by becoming personally involved with a patient and actively trying to ensure that the patient received Zorac Gel, had failed to maintain a high standard of ethical conduct and ruled a breach of the Code. A breach was also ruled because the pharmacy department concerned had not been informed about the product prior to its promotion, contrary to hospital policy.

COMPLAINT

A hospital pharmacy manager complained about the conduct of a representative from Novex Pharma. The representative had arrived in the pharmacy department with an outpatient and a prescription for the patient for Zorac Gel.

The complainant spoke to the representative and confirmed with her that she had not spoken to the pharmacy or left any product information before promoting Zorac Gel, contrary to hospital policy.

The complainant said that she asked the patient and the representative to take a seat whilst she spoke to the prescriber about the entry of a new product into the hospital formulary. When the complainant went back and called the patient to explain about obtaining the product the representative stood up to approach the counter.

The complainant had since had a letter of apology from the representative but considered it unacceptable that a representative brought a prescription for a new product to the pharmacy.

The matter was taken up by the Authority with Novex Pharma in the first instance and was subsequently taken up also with Allergan Ltd, whose product Zorac Gel was.

Case AUTH/623/10/97

Novex Pharma

RESPONSE

Innovex (UK) Limited replied on behalf of Novex Pharma and explained that Novex Pharma, in this instance, was not Novex Pharma Limited which was a member company of the ABPI and a subsidiary of Innovex (UK) Ltd. Novex Pharma was the name of one of Innovex's syndicated sales teams which was selling up to three products from potentially different pharmaceutical companies. The representatives of this team were selling Zorac Gel on behalf of Allergan in general practice and hospitals. The line manager of the representative in question was employed by Innovex - there were no direct management links to Allergan.

Innovex stated that the Novex representative in question was waiting to see the consultant dermatologist in his waiting room and had been engaged in general conversation with a patient also waiting to see the consultant. During the conversation the patient revealed that she was there to see the doctor about psoriasis and the representative expressed an interest in that disease area. Innovex stated that it should be noted that no promotion of the product took place during this conversation.

Innovex stated that the patient was called in to see the doctor and some minutes later the Novex representative was asked to join them and enlighten the doctor, in the presence of the patient, as to the benefits of the product she was promoting for the treatment of psoriasis. The representative presented the product directly to the doctor whilst the patient was in the same room. A prescription was then issued by the doctor and the representative accompanied the patient to the pharmacy where the pharmacist was made aware by the representative that a prescription had been written for Zorac for the patient. The pharmacist took exception to this and apologies ensued, both verbally and in writing.

Innovex submitted that there was never any intention on the part of the representative to promote the product either directly or indirectly to the patient. In fact the main hospital pharmacy department had previously been visited by the representative and the prescribing information for Zorac relayed.

The representative had passed the ABPI Medical Representatives examination with Innovex over two years ago and held the Code in the highest regard. This was the

first time her conduct had been called into question.

Innovex submitted that the representative had acted in a somewhat naïve fashion, which she now regretted. The company pointed out, however, that the representative acted on the direct wishes of the doctor involved, which must have had an impact on her judgement of the situation.

Innovex emphasised that the representative in question did not act on any instructions from Allergan.

Case AUTH/638/11/97

Allergan Ltd

RESPONSE

Allergan stated that it had already been made aware of the complaint by Novex Pharma and confirmed that the representative concerned had been warned that this type of behaviour was not acceptable and had undergone a retraining programme. The company had issued a memo to all Allergan, and Innovex sales forces contracted to Allergan, stressing the importance of adhering to all aspects of the Code and drawing specific clauses to their attention. A letter of apology had been sent to the pharmacist.

Allergan explained that previously it had only a small specialist hospital sales team and this was the first time it had employed the services of an external sales force. The Innovex sales force promoted products for several companies. Whilst product training and promotional material approval was carried out by Allergan, training with respect to the ABPI Code was conducted by Innovex. The company did of course verify before contracting the Innovex sales force that the necessary training and compliance with the Code was established and adhered to by Innovex. The company requested clarification on Clause 15 with regard to representative conduct bearing in mind that they were syndicated to several companies and were full time employees of Innovex. Nonetheless the company apologised for the incident and could only stress that neither Allergan nor Innovex had instructed the representative to behave in this manner.

Cases AUTH/623/10/97 & AUTH/638/11/97

PANEL RULING

The Panel noted the requirements of the supplementary information to Clause 15 headed "Contract representatives" which stated that companies employing contract representatives were responsible for their conduct and must ensure that they complied with the provisions of this and all other relevant clauses in the Code. The Panel noted that the 1998 edition of the Code would include an amendment to the supplementary information to more accurately describe the possible relationships. The new supplementary information would read "Companies employing or using contract representatives..." and this would hopefully make it clearer that it was the pharmaceutical company whose products were being promoted which was responsible for the conduct of contract representatives.

The Panel noted that at the time of the receipt of the complaint it was not clear as to the relationship between Novex Pharma and Allergan. It had been assumed that Novex Pharma Limited was involved and that it was promoting the product in its own right even though Allergan was the marketing authorization holder. Novex Pharma had been asked to explain the relationship and, following receipt of the response from Innovex, it had become clear that Novex Pharma was not acting as pharmaceutical company in its own right but was acting as a contract representative company to promote Zorac Gel on behalf of Allergan. The Panel therefore considered that, taking into account the supplementary information to Clause 15, Allergan was responsible for the conduct of the contract representatives as far as the Code was concerned. Only Allergan was therefore potentially in breach of the Code and only Case AUTH/638/11/97 need be considered in detail. Novex Pharma was not responsible under the Code. There could therefore be no breach in Case AUTH/623/10/97 and the Panel so ruled.

Case AUTH/638/11/97

The Panel noted that the representative had talked to the patient in the waiting room before the patient had been called in to see the consultant dermatologist. The representative had then been asked to go into the consulting room to talk to the consultant in the presence of the patient. In the Panel's view, the representative must have given the patient the impression that she had a product for psoriasis for this to have happened. The representative had then accompanied the patient to the pharmacy department and had tried to play a role in ensuring that the prescription for Zorac Gel was filled. The Panel noted that Zorac Gel was not on the hospital formulary. The representative had previously visited the main hospital pharmacy department to detail Zorac Gel but had confirmed with the complainant that she had not similarly visited the pharmacy department in question.

The Panel considered that the representative's conduct was unacceptable. The representative, by becoming personally involved with a patient and actively trying to ensure that the patient received a prescription for Zorac Gel, had failed to maintain a high standard of ethical conduct. The Panel ruled a breach of Clause 15.2. In addition, the Panel noted that, contrary to hospital policy, the representative had failed to ensure that the relevant pharmacy department had been informed about Zorac Gel before she had promoted it. A breach of Clause 15.4 was ruled.

Complaint received **13 October 1997**

Cases completed **23 December 1997**

CASE AUTH/624/10/97

LILLY v ORGANON

Zispin press release

An article in The Scotsman with the headline "Is it proper to use sex to sell the new happy drug?" referred to a press release concerning the launch of Zispin by Organon which was headed "Sex please, I'm on Zispin!". Eli Lilly complained that from what was said about the press release it appeared that the claims made in it about Prozac, Lilly's product, resulted in adverse publicity in the lay press. Lilly said it appeared that the press release might have been presented in such a way that it could encourage members of the public to ask their doctor to prescribe a specific medicine. The use of the press release promoted a prescription only medicine to the general public and, further, such publicity had the potential to discredit and reduce confidence in the industry.

The Panel noted that the document headed "Sex please, I'm on Zispin!" was neither factual nor presented in a balanced way. It was very positive for the product and made a number of statements inappropriate for information to the general public. The Panel considered that it would encourage members of the public to ask their doctors to prescribe a specific medicine and ruled a breach of the Code. The Panel did not consider that the press release had discredited and reduced confidence in the industry and so no breach of Clause 2 was ruled. The Panel did, however, rule a breach because high standards had not been maintained.

An article in The Scotsman, 24 September 1997 with the headline "Is it proper to use sex to sell the new happy drug?", referred to the launch of Zispin (mirtazapine) being announced by Organon Laboratories Ltd via a press release with the heading "Sex please, I'm on Zispin!". The article referred to Zispin as the pill to replace Prozac (Eli Lilly & Company Limited's product) and stated that Zispin was better than Prozac at combating the effects of depression while carrying fewer serious side effects.

COMPLAINT

Lilly said that it was understandable that the launch of a new medicine would be accompanied by a press release issued by the manufacturer. However in this instance it appeared that claims made about Lilly's product resulted in adverse publicity in the lay press with no evidence presented to substantiate the claims. The press release was reported to make claims regarding the difference in sexual side effects between mirtazapine and Prozac, as well as making claims that mirtazapine was more efficacious than Prozac.

Lilly stated that from what was reported about the press release, it appeared that it might have been presented in such a way that its purpose could be to encourage members of the public to ask their doctors to prescribe a specific medicine. The company referred to the article in The Scotsman which stated that:

"The use of sex to generate interest in the drug was deplored yesterday by a lawyer who represents people who have been harmed by antidepressants".

and

".... there are regulations in Britain which prevent drugs being marketed directly to patients but drug companies get around these by issuing positive press releases which get picked up by the media. Patients read the stories and start demanding the drugs".

Lilly alleged that the use of the press release to promote a prescription only medicine to the public was in breach of Clause 20.2 of the Code. Further, such publicity had the potential to discredit and reduce confidence in the pharmaceutical industry. A breach of Clause 2 of the Code was alleged.

RESPONSE

Organon acknowledged that in retrospect it had become apparent that the distribution of the press release was inappropriately controlled. Moreover the Code of Practice signatories incorrectly assumed that the briefing was intended for the medical press only and thus failed to acknowledge the full extent of its distribution. A list of health correspondents who received the press release was provided. This included the medical and pharmaceutical press as well as the lay press.

Organon submitted that although the content of the press pack was both factual and balanced, the title was clearly contentious. However it was unable to ignore an important aspect of both depression and antidepressant therapy, namely sexual dysfunction. It was important to note that the text made no mention of Prozac but rather fluoxetine. Nor did it make any direct comparison between the sexual side effects of mirtazapine and fluoxetine. It was thus most unfortunate that Prozac was vilified in the press by journalists in their pursuit for sensationalism.

Organon had no prior knowledge of the article in The Scotsman and certainly had no editorial influence or control. In addition it was impossible to divert or indeed stop the flow of information from the medical press to the lay press. Alternative sources of information such as the Internet further compounded the problem. The Freedom of Information Act in the United States of America had facilitated the readily accessible extensive information on Zispin internationally. Details about Zispin had appeared in MIMS.

Organon submitted that the intention of the press release was not to encourage members of the public to ask their doctors to prescribe Zispin but rather to inform the audience of a new antidepressant. The company acknowledged that it had clearly been naïve in the disclosure of information on a prescription only medicine and apologised unreservedly for its inadvertent carelessness allowing the possible breach of Clause 20.2. It was certainly not the company's aim to bring the pharmaceutical industry into disrepute thereby breaching Clause 2. The company undertook to take immediate

steps to ensure that its copy clearance procedure was improved in order to remove the potential for future difficulties.

PANEL RULING

The Panel noted that complaints about articles in the press were judged on the information provided by the pharmaceutical company or its agent and not on the content of the article itself.

The Panel noted that the company signatories had incorrectly assumed that the briefing was intended for medical press only. The press release had been sent to the lay press as well as medical and pharmaceutical press. The Panel was concerned that Organon had not been aware of the full extent of its distribution. Pharmaceutical companies were responsible for the activities of their agents. It was very important that pharmaceutical companies were aware of materials etc distributed by their agents.

The Panel noted that the press release consisted of three documents. These were headed "Sex please, I'm on Zispin!", "Zispin: the clinical trial data", and "Antidepressants and their mechanisms of action". It appeared on paper with an agency name and address.

The Panel noted that the document headed "Sex please, I'm on Zispin!" referred to the fact that sexual dysfunction was reported in 34-75% of patients treated with fluoxetine. Conversely, statements regarding the side-effect profile of Zispin were very positive, concentrating on the side-effects that the product did not have compared with other antidepressants, as opposed to those that it did. It was stated that sexual dysfunction was not a side-effect of Zispin. The document headed "Zispin: the clinical trial data" stated that some of the side-effects associated with amitriptyline occurred significantly less often in Zispin treated patients. Typical serotonergic side-effects such as might occur in patients receiving fluoxetine occurred at less than placebo level in Zispin treated patients. The Panel noted that the SPC for Zispin stated that increase in appetite and weight gain were commonly reported (>1/100) as was drowsiness/sedation, generally occurring during the first few weeks of treatment.

The Panel noted that, as the press release had been made indirectly available to the general public, Clause 20.2 of the Code applied. This required that information for the general public must be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their doctors to prescribe a specific medicine.

The Panel considered that the document headed "Sex please, I'm on Zispin!" was not factual and nor was it presented in a balanced way. The press release was very positive for the product. It referred to Zispin as a "unique new antidepressant" and stated that "It offers people with depression a new treatment option which is not only more effective than fluoxetine, but does not cause many of the sexual problems associated with most other antidepressants". The press release stated that Zispin was shown to be more efficacious than fluoxetine in a trial and stated that the results "... represent an absolute advance in treatment". The press release stated that Zispin also appeared to be "safe in overdose".

Overall, the Panel considered that the press release was not presented in a balanced way and would encourage members of the public to ask their doctors to prescribe a specific medicine. A breach of Clause 20.2 of the Code was ruled.

With regard to the alleged breach of Clause 2 of the Code, the Panel noted that a ruling of this clause was a sign of particular censure and was reserved for such circumstances. The Panel did not consider that the material was in breach of Clause 2 of the Code and no breach of that clause was ruled. The Panel did, however, consider that the use of the heading "Sex please, I'm on Zispin!" meant that the company had failed to maintain a high standard as required by Clause 9.1 of the Code. The Panel therefore ruled a breach of Clause 9.1.

The Panel noted that Lilly had not cited a clause number as required by Paragraph 5.2 of the Constitution and Procedure in relation to the allegation that no evidence had been provided in relation to statements about its product. Organon had not responded to this point. The Panel therefore decided not to make a ruling. Lilly would have to submit another complaint if it wished to pursue this allegation.

Complaint received **14 October 1997**

Case completed **10 December 1997**

CASE AUTH/625/10/97

GENERAL PRACTITIONER v SHIRE

Promotion of Calcichew D_3 Forte

A general practitioner complained that the statement "Raising serum calcium slows age-associated bone loss" in a leaflet relating to Calcichew D_3 Forte issued by Shire was misleading. If dietary intake was adequate then additional calcium would not have any effect on age-associated bone loss. Bone loss could only be slowed by raising serum calcium in those who had a deficient diet.

In the Panel's view the implication of the statement "Raising serum calcium slows age-associated bone loss" was that raising serum calcium in all patients would slow age-associated bone loss. This was not the case. Supplemental calcium only slowed age-associated bone loss in those people whose dietary intake was inadequate. The statement was misleading and was ruled in breach of the Code.

A general practitioner complained about a leaflet for Calcichew D_3 Forte (M003/0009) issued by Shire Pharmaceuticals Ltd. The leaflet was entitled "Inner Strength" and examined the role of calcium and vitamin D in the maintenance of healthy bones in the elderly. Shire Pharmaceuticals, although not a member of the ABPI, had agreed to comply with the Code.

COMPLAINT

The complainant alleged that the statement "Raising serum calcium slows age-associated bone loss" was misleading. The complainant's understanding of the evidence was that, given that an adequate dietary intake was present, additional calcium made no difference and therefore raising calcium in this situation did not have any effect on age-associated bone loss. The complainant was sure that bone loss could only be slowed by raising serum calcium in those who had a deficient diet.

The complainant advised his patients to try and maintain a 1500mg intake of calcium a day which was his understanding of the current recommended levels.

The complainant said that if he was incorrect, he would certainly be grateful to hear that this was so - however, if not, he wondered whether Shire should add to the end of the statement "... in people whose dietary intake is not sufficient".

RESPONSE

Shire said that in support of its claim the context of the piece clearly identified that reduced bone strength was associated with increasing age and reduced levels of calcium and vitamin D. The statement in question examined the effects of raising serum calcium levels in these patients and these patients alone. The statement, although supported by a reference, should therefore be considered in context of the overall piece and not on a stand alone basis.

Shire said that currently the medical profession, led by the Scientific Advisory Board of the National Osteoporosis Society, accepted that for men and women over the age of 65 the average daily intake of elemental calcium should be 1500mg as the complainant correctly identified. However, Cumming (1990) in a meta-analysis of retrospective trials showed that the mean daily intake of calcium in post menopausal women ranged from 403mg to 1308mg. These trials studied over 4,900 women and corroborated data obtained by Chapuy *et al* (1992) who studied the average daily calcium intake of 3270 elderly institutionalised women and discovered that the mean daily calcium intake was less than 515mg. Shire said that, in addition, a more recent study of ambulatory men and women over the age of 65, who were enrolled in a three year double blind placebo controlled study, identified that neither men nor women at the commencement of the trial had calcium intakes of 1500mg daily (Dawson Hughes, (1997)).

Shire considered that for most elderly patients the average daily intake of calcium was below the recommended dose of 1500mg and, therefore, with this in mind, its statement should be considered appropriate.

Shire accepted that out of context the statement might appear misleading, but evidence obtained by Reid *et al* (1993) in a study of 122 late menopausal normally healthy women who were asked to take either 1000mg of calcium daily or placebo for two years showed increased bone density at the lumbar spine and reduced bone loss by 67% at wards triangle and by 43% for total body BMD when compared with placebo. Shire stated that in this study the effects of calcium on bone were seen irrespective of the patients' normal daily intake of calcium which supported the claim in its literature.

In addition to the clinical support provided to substantiate the statement, Shire fully advocated dietary and exercise advice to all patients suffering from, or who were at risk of, osteoporosis. This could be seen on page four of the piece where Shire had referenced osteoporosis therapy options as defined by Francis *et al* (1994). Shire considered that this further substantiated its claim, and also addressed the secondary issue of dietary intake which the complainant addressed. Shire provided a copy of its patient dietary and exercise leaflet which was written by a GP and endorsed by the National Osteoporosis Society.

Shire considered its literature provided valuable data regarding the nature of bone loss in elderly patients with falling levels of calcium and vitamin D. The piece in question supported the use of Calcichew D_3 Forte in these patients only whilst advocating dietary and exercise advise for all patients who fulfilled the criteria defined by the disease and Shire's product licence.

PANEL RULING

The Panel noted that the leaflet examined the role of calcium in the maintenance of healthy bones in the

elderly. Page two of the leaflet contained the statement "There is an age associated loss of bone strength as a result of a decrease in Vitamin D and calcium levels". On the facing page was the statement in question "Raising serum calcium slows age-associated bone loss". In the Panel's view, however, the two statements, and thus the concept of raising serum calcium levels from a decreased level, were not explicitly linked.

The Panel noted that there was evidence to show that, in patients whose daily calcium intake was inadequate (less than 1500mg), calcium supplements were effective in slowing bone loss (Cumming (1990); Chapuy *et al* (1992); Reid *et al* (1993)). The Panel accepted that many elderly people might have an inadequate daily intake of calcium. In the Panel's view, however, the implication of the statement "Raising serum calcium slows age-associated bone loss" was that raising serum calcium in all patients would slow age-associated bone loss. This was not the case, supplemental calcium only slowed age-associated bone loss in those patients whose dietary intake was inadequate. The Panel considered that the statement was misleading and ruled a breach of Clause 7.2.

Complaint received 15 October 1997

Case completed 4 December 1997

CASES AUTH/626/10/97 AND AUTH/627/10/97

GENERAL PRACTITIONER v BRISTOL-MYERS SQUIBB AND SANOFI WINTHROP

Meeting in Brussels

A general practitioner complained about a meeting in Brussels organised jointly by Bristol-Myers Squibb and Sanofi Winthrop. All of the speakers were from the UK, it was not an international conference and , in the complainant's view, it was inappropriate to hold it abroad. There was no course fee, return airfare would be paid and hotel accommodation and food would be provided. The complainant judged that the cost would be more than he would spend himself in attending such a meeting which, he submitted, was thinly veiled promotion in a luxurious foreign setting.

The Panel noted that the Code permitted the provision of appropriate hospitality provided that this was secondary to the purpose of the meeting and was appropriate and not out of proportion to the occasion. Meetings could be held outside the UK but the impression created by the arrangements had to be kept in mind. In the Panel's view the programme should attract delegates and not the venue.

The Panel questioned why the meeting had been held in Brussels when all the participants were from the UK. The Panel considered that the meeting did not justify the two nights' accommodation which were provided. The first night's accommodation was reasonable because the meeting started at 9am. It appeared to the Panel that the second night's accommodation had been provided merely because Brussels as a venue meant that it was difficult for delegates to return home on the same day. In the Panel's view the cost of the meeting exceeded the level which recipients would normally adopt when paying for themselves. The Panel considered that the arrangements for the meeting were unacceptable and ruled that the Code had been breached.

A general practitioner submitted a complaint about a meeting held in Brussels from 31 October to 2 November 1997 which had been organised jointly by Bristol-Myers Squibb Pharmaceuticals Ltd and Sanofi Winthrop Limited.

COMPLAINT

The complainant's objections related to Clause 19.1 of the Code. The meeting was held in a hotel in Brussels, when all the speakers were from Britain. This was not an international conference and, in the complainant's view, it was therefore disproportionate to hold it abroad.

The complainant stated that he had spoken to the agency arranging the meeting and was told that there was no course fee, his return airfare from an English airport of his choice to Brussels would be paid and free hotel accommodation and food would be provided. PGEA accreditation would also be awarded. The complainant judged that this was more than he would spend himself in attending such a meeting. He submitted that three days and two nights in a hotel was disproportionate for a one day meeting on a Saturday which started at 8.30am and finished at 3.45pm on the same day.

The complainant pointed out that the opening address of the meeting was about a medicine called irbesartan, which was so new that it did not appear in the current edition of the British National Formulary or in the ABPI Compendium of Data Sheets and Summaries of Product Characteristics. He would not be surprised to hear that it was made by Bristol-Myers Squibb/Sanofi Winthrop and submitted that this was thinly veiled promotion provided free of charge in a luxurious foreign setting - inappropriately so.

When writing to the companies the Authority requested them to comment on whether Clauses 2, 3.1 and 9.1 of the Code had been breached.

RESPONSE

Bristol-Myers Squibb and Sanofi Winthrop submitted a joint response to the complaint. They confirmed that the meeting referred to was jointly sponsored by Bristol-Myers Squibb and Sanofi Winthrop and said that it was one of a number of such meetings being held, in either Dublin or Brussels, for UK general practitioners.

The companies confirmed that these meetings, which had PGEA approval for 4 hours (disease management), would include a presentation on irbesartan (Approvel), which

was licensed in the UK for the treatment of hypertension.

Bristol-Myers Squibb and Sanofi Winthrop submitted that the letter of invitation and reply paid acceptance card and accompanying provisional agenda for the meeting did not suggest that this would be an international conference. All of the attendees were general practitioners from the UK and a list of the delegates was provided. The speakers were all from the UK.

Bristol-Myers Squibb and Sanofi Winthrop submitted that it was not inappropriate to take this group to Brussels as this was a venue which could be easily reached from most of the UK. The cost of travel to Brussels was similar to the cost of internal flights or first class rail fares within the UK. For example, a first class rail fare from Glasgow to London was £199 return; and a first class return fare from London to Manchester would cost £135. Details of the cost of flights to Brussels for this meeting were provided.

Bristol-Myers Squibb and Sanofi Winthrop stated that the decision to conduct these meetings at venues in Brussels and Dublin was made on the basis of favourable cost comparisons with comparable UK venues. Details of the costs for these meetings as estimated in June 1997 when the decision to hold these meetings abroad was approved by both companies, the revised anticipated costs for the specific meeting in question which showed that the cost per delegate for this meeting was £542 and, for the purpose of comparison, quotations received for a variety of comparable UK venues, were provided. The quotations for the cost of holding such a meeting at a UK venue ranged between £374 - £684 per head. The total cost of £542 per delegate was within this range.

Bristol-Myers Squibb and Sanofi Winthrop submitted that as the cost of travel and accommodation for a Brussels meeting was not dissimilar to the cost for a UK venue, they did not believe that it was "disproportionate or inappropriate" to hold this meeting in Brussels.

Bristol-Myers Squibb and Sanofi Winthrop reiterated that the costs were not dissimilar to the costs of attending such a meeting in a UK venue and that the hotel selected in Brussels was one at a level which most doctors would be prepared to pay for themselves. The companies did not agree that the venues offered were "in a foreign luxurious setting" but rather were at middle range, business style hotels at cities in close proximity to the UK.

The companies provided a schedule of events and details of flights for the meeting. Attendees were expected to arrive at the hotel in the evening on Friday. It was considered unlikely that many attendees would arrive before 7.30pm on Friday. Sixty-seven of the 100 delegates would arrive at the hotel between 7.30pm and 8.30pm on Friday evening. All of the delegates would have left the hotel by lunchtime on Sunday. The duration of the meeting might more correctly be expressed as two nights and one day rather than three days and two nights.

Bristol-Myers Squibb and Sanofi Winthrop submitted that the meeting had a clear educational content and had received PGEA approval.

The detailed schedule of events indicated that the agenda was centred on the scientific meeting. Attendees would arrive at different times on Friday evening. A "running buffet" was available to provide supper on Friday. There were no other arrangements for Friday.

As shown in the provisional agenda submitted by the complainant, the meeting was scheduled to start on Saturday at 8.30am. There was a very full agenda and it concluded with "round table" discussions. The provisional agenda indicated a 3.45pm close to the meeting as alluded to by the complainant. The final agenda was provided.

After the meeting attendees were invited to stay for dinner and accommodation on Saturday night. The dinner was held at a local museum at a cost of £75 per delegate including transfers and wine. Bristol-Myers Squibb and Sanofi Winthrop submitted that this hospitality was secondary to the main purpose of the meeting and was not inappropriate to the standing of the invitees. In addition, this hospitality was provided at a level which most doctors would be prepared to pay for themselves. The costs for the dinner were included in the breakdown of the total delegate costs.

Attendees were booked on return flights on Sunday morning. All would have left the hotel by lunchtime. Apart from dinner on Saturday night and the inclusive breakfast on Sunday morning there were no other arrangements made for attendees by the two companies. In particular, lunch on Sunday would not be paid for by the sponsors. All attendees received, on arrival at the hotel, clear instructions that the companies would not be paying any "extras" at the hotel.

Bristol-Myers Squibb and Sanofi Winthrop submitted that two nights' accommodation was not inappropriate for this meeting. They therefore did not believe that the duration of stay was inappropriate and submitted that the hospitality provided was secondary to the main purpose of the meeting.

In relation to Clause 3.1 of the Code, Bristol-Myers Squibb and Sanofi Winthrop stated that irbesartan was licensed in the UK for the treatment of hypertension. The licence was granted on 27 August 1997.

Letters of invitation for these meetings of UK general practitioners were sent by mail on 22 July 1997. The letter of invitation included the provisional agenda for the meeting. All of the meetings were scheduled to be held, and in fact were held, after the granting of the product licence. The letter of invitation and the provisional agenda sent to the general practitioner were not, in themselves, promotional. There was therefore no promotional activity prior to the receipt of the product licence and therefore no breach of Clause 3.1.

In relation to Clause 9.1 of the Code, Bristol-Myers Squibb and Sanofi Winthrop submitted that the letter of invitation and provisional agenda sent to general practitioners made it very clear that the meeting would be sponsored by Bristol-Myers Squibb and Sanofi Winthrop. The letterhead bore both corporate logos, the heading to the letter bore both company names and the first line of the invitation made it clear that the invitation was on behalf of both companies.

In addition the provisional agenda which invitees received also indicated that the meeting was sponsored by both companies and it was clear that the presentation on irbesartan was to be given by a doctor with affiliation to one of the sponsoring companies.

The reply paid invitation acceptance form also clearly

indicated corporate sponsorship. Bristol-Myers Squibb and Sanofi Winthrop did not agree that this was "thinly veiled promotion". There was no promotional content in the materials used. Sponsorship of the meeting was explicit in all of the associated materials:

This meeting was of high standard and respected the standing of the invitees and this activity did not represent a breach of Clause 9.1.

In conclusion Bristol-Myers Squibb and Sanofi Winthrop stated this meeting and other similar meetings would include UK general practitioners. All the speakers would be from the UK. The meeting was not held in a "foreign luxurious hotel". The meeting was held in Brussels at a business grade hotel, the expense of which most doctors would be willing to pay for and the hospitality afforded was secondary to the main purpose of the meeting.

There had been no attempt promote irbesartan prior to the grant of its licence.

All of the materials sent to invited doctors had made the corporate sponsorship of this meeting explicit and the materials had been of a high standard and respectful of the standing of recipients.

Bristol-Myers Squibb and Sanofi Winthrop did not therefore believe that this activity had breached Clauses 19.1, 3.1, or 9 of the Code. Nor did this activity bring discredit upon, or reduce confidence in, the pharmaceutical industry and therefore Clause 2 of the Code had not been breached.

PANEL RULING

The Panel noted that Clause 19.1 of the Code permitted companies to provide appropriate hospitality to members of the health professions and appropriate administrative staff in association with scientific and promotional meetings, scientific congresses and other such meetings. Hospitality must be secondary to the purpose of the meeting and the level of hospitality offered must be appropriate and not out of proportion to the occasion.

The Panel noted that the Code did not prevent companies from holding meetings for UK health professionals at venues outside the UK. The supplementary information to Clause 19.1 stated that the impression created by the arrangements for any meeting must be kept in mind. In the Panel's view the programme should attract delegates and not the venue.

The Panel noted that PGEA approval had been obtained. The supplementary information to Clause 19.1 of the Code stated that the fact that a course was PGEA approved did not mean that the arrangements for the meeting were automatically acceptable under the Code.

The Panel noted that the meeting in question was a GP launch meeting for irbesartan. The letter of invitation was headed "Bristol-Myers Squibb/Sanofi Symposia on Risk Reduction in Hypertensive Patients: Practical Responses to Today's Challenges". The Panel noted that there were differences in timings between the agenda provided by the complainant and the final agenda provided by the companies. In particular the agenda provided by the complainant showed the meeting finishing at 3.45pm whereas the final agenda showed a 5pm finishing time. The meeting in question commenced at 9am. Following the Chairman's welcome there was a 15 minute presentation entitled "Irbesartan: The Profile of a new approach to hypertension" given by the Director of Cardiovascular, Bristol-Myers Squibb/Sanofi Winthrop. The remainder of the programme related to issues in the management of hypertension. There were two breaks of 30 minutes for coffee or tea and a lunch break of one hour. The Panel considered that the educational content was not unreasonable.

The Panel noted that the estimated cost of the meeting in question was £542 for each delegate. This included economy flight, airport transfers, two nights' accommodation and breakfast, and the cost of two dinners and one lunch. The Panel noted that the comparable costs of holding the meeting at UK hotels were London £684, Edinburgh £499, Cheshire £374, Warwick £386.

The Panel queried why the meeting had been held in Brussels when all the delegates and speakers were from the UK. The meeting itself did not justify two nights' accommodation as there was no educational programme on the Sunday. The Panel considered that it was not unreasonable for companies to provide accommodation on the evening prior to a meeting which started at 9am. In the case in question, however, it appeared to the Panel that the second night's accommodation had been provided merely because Brussels had been chosen as the venue which meant that it was difficult for delegates to return home on the Saturday evening. If the meeting had been held in the UK return travel on the Saturday would have been more likely.

The Panel noted that the meeting in question was one of nine UK GP launch meetings to be held by Bristol-Myers Squibb and Sanofi Winthrop between 10 October 1997 and 15 February 1998 at various hotels in Brussels and Dublin. As nine meeting were to be held the Panel considered that it would have been possible to organise them regionally at various venues in the UK and invite doctors from each particular area to attend. Other venues in the UK could have been chosen which might not have been as expensive as the meeting in Brussels and which for many delegates would not have necessitated two nights' accommodation.

In the Panel's view the costs of the meeting in question (£542 per head) exceeded that level which the recipients would normally adopt when paying for themselves.

The Panel considered that the arrangements for the meeting were unacceptable. The Panel therefore ruled a breach of Clause 19.1 of the Code.

The Panel noted that there was no promotional activity prior to receipt of the product licence and hence ruled no breach of Clause 3.1 of the Code. The Panel considered that as the educational content was not unreasonable there was no breach of either Clause 2 of the Code or Clause 9.1.

All of the rulings applied to both companies.

Complaint received **17 October 1997**

Case completed **7 January 1998**

CASE AUTH/628/10/97

WYETH v GALDERMA

Tetralysal leavepiece

Wyeth complained about a leavepiece for Tetralysal issued by Galderma which contained the claim "Efficacy comparable to minocycline and doxycycline". Wyeth marketed minocycline as Minocin. Wyeth alleged that the studies upon which the claim was based used sub-optimal and non licensed regimens of minocycline. It was therefore unreasonable for Galderma to claim that its product was comparable to minocycline on the basis of those studies.

The Panel noted that the detail aid was for use in the UK and considered that any claims and comparisons made in it should be relevant to the UK market. The studies used by Galderma to support its claim were based on dosages of minocycline recommended in France which, from the third week of therapy on, were below those approved in the UK. The Panel considered that the claim was misleading and had not been substantiated and ruled it to be in breach of the Code.

Wyeth complained about a Tetralysal detail aid (TE:VA:0197 (McMCA)) issued by Galderma (UK) Limited. Galderma, although not a member of the ABPI, had nevertheless agreed to comply with the Code. The detail aid contained the claim "Efficacy comparable to minocycline and doxycycline" which was referenced to "Data on file Galderma". Wyeth marketed minocycline (Minocin).

COMPLAINT

Wyeth alleged that the studies used by Galderma to support the claim, "...comparable to minocycline...", which were by Cunliffe *et al* and Schollhammer and Alirezai, both used minocycline in doses lower than the UK licensed dose. The Cunliffe study used minocycline 100mg a day reducing to 100mg on alternate days after 2 weeks followed by 100mg on alternate days for 10 weeks. The Schollhammer study used minocycline 100mg a day for 2 weeks reducing to 50mg a day for 10 weeks or minocycline 100mg a day for 2 weeks followed by 100mg on alternate days for 10 weeks. Wyeth pointed out that neither of these regimens were licensed for minocycline in the treatment of acne. The UK summary of product characteristics for minocycline clearly stated "Acne: 50mg twice daily: Treatment should be continued for a minimum of 6 weeks.".

Wyeth stated that both studies administered sub-optimal and non licensed regimens of minocycline. It was therefore unreasonable for Galderma to claim that its product was comparable to minocycline based on these studies. It was alleged that the claim was in breach of Clauses 7.2 and 7.3 of the Code.

RESPONSE

Galderma stated that the claim that Tetralysal's efficacy was comparable to minocycline and doxycycline was based on studies which were carried out in France using French recommended dosages.

Galderma pointed out that there were currently several different dosage regimens for Tetralysal and minocycline in Europe. These different dosage regimens were only guidelines and prescription policy was set by the individual doctors. An example of this was Wyeth's own French promotional material providing doctors with a choice of regimens depending on whether they preferred the 100mg or 50mg form.

Galderma submitted that the market for a product such as Tetralysal was not extensive enough to justify the company carrying out studies within each individual country in Europe. Therefore, Galderma decided to sponsor the studies referred to above, involving a number of doctors in different countries including the UK, to give general guidance as to the efficacy of the respective drugs. The studies were based on the French dosages as France was currently the largest European market for Galderma and a significant market for Wyeth products (supporting IMS sales data was provided).

Galderma did not accept Wyeth's view that the dosages used for the studies were sub-optimal. The dosages that Wyeth stated were sub-optimal were in fact the dosages currently recommended by Wyeth in France. (Galderma supplied the current prescribing information and promotional material for the Wyeth minocycline products). Galderma said that if Wyeth was claiming that the dosages used for the studies were sub-optimal, it was admitting that its product as distributed in a large European market was, in fact, sub-optimal. Galderma found this rather puzzling and had assumed that Wyeth could not object to scientific comparison based on a dosage regimen which it recommended for France.

Galderma said that because of the general nature of the studies on which it had relied, it had been very careful regarding the statements in its material. Galderma only advertised Tetralysal as being "comparable" to minocycline. It had not made a more detailed claim that the product had the same or better efficacy and had not reproduced the tables from the studies showing that Tetralysal had slightly better results, subject to statistical variation. Galderma said that it made this statement deliberately general in nature so as not to be misleading. In addition, the company did not consider that the promotional material was misleading because it was aimed at and made available to doctors only.

Galderma did not consider that its promotional material was in breach of Clauses 7.2 and 7.3. In the company's view the studies supporting the claims were a fair, balanced and accurate comparison, despite the different dosages in various markets.

PANEL RULING

The Panel noted that the detail aid in question was for use in the UK. The Panel considered, therefore, that any

claims and comparisons contained therein had to be relevant to the UK market.

The Panel examined the studies provided by Galderma to support its claim that Tetralysal had efficacy comparable to minocycline. The dose of minocycline used in the studies was 100mg a day for two weeks reduced to 50mg a day, or 100mg on alternate days, for the next ten weeks. This was the recommended dosage of minocycline in France. The Panel noted that in the UK the recommended dosage regimen for Minocin in the treatment of acne was 50mg twice daily for a minimum of six weeks (ref ABPI Compendium of Data Sheets and Summary of Product Characteristics). The claim for comparable efficacy of Tetralysal and minocycline was thus based on studies using, from week three onwards, doses of minocycline below those recommended in the UK. The Panel considered that the claim was misleading and had not been substantiated. The Panel ruled breaches of Clauses 7.2 and 7.3 as alleged.

Complaint received **21 October 1997**

Case completed **7 January 1998**

CASE AUTH/635/10/97

HOSPITAL PHARMACIST v MERCK SHARP & DOHME

Letters in Timoptol-LA referral pack

A hospital pharmacist complained about two letters in a Timoptol-LA referral pack from Merck Sharp & Dohme. It was alleged that a "Dear Ophthalmologist" letter and a sample referral letter for ophthalmologists to send to general practitioners might be disguised promotion. In addition, it was alleged that it was incorrect to say that Timoptol-LA cost the same as the twice daily formulation as generic timolol eye-drops were cheaper. The complainant acknowledged that Timoptol-LA was the same price as Timoptol but it was not the same price as the generic which was important for GPs.

The Panel considered that the pack was promotional material as acknowledged by Merck Sharp & Dohme. The Panel did not accept that the "Dear Ophthalmologist" letter was disguised as it was a typical "Dear Doctor" letter promoting a product. No breach was ruled in that regard. The Panel noted that the sample GP referral letter which was the subject of the complaint was relevant only where all patients were being switched from one Merck Sharp & Dohme product, Timoptol, to another, Timoptol-LA. No other products were involved. The Panel considered that the letter was promotional. Timoptol-LA was mentioned in every sentence, each time in block capitals. The phrase "New TIMOPTOL-LA brings all the established benefits of TIMOPTOL to glaucoma patients..." was considered to go beyond the factual and practical issues about the therapy switch and was inappropriate for a letter intended to go to general practitioners from an ophthalmologist. The letter was ruled in breach because it would amount to disguised promotion if used and high standards had not been maintained. No breach was ruled in relation to the cost of changing therapy as the claim was correct. In the context of the pack there was no need to consider the cost of the generic product.

A hospital pharmacist complained about two letters which were contained in an Ophthalmologist's Primary Care Referral Pack for Timoptol-LA (timolol) issued by Merck Sharp & Dohme Limited. The first letter was a sample GP referral letter (ref 08-98TOTX.97.GB.52027. LB.5c.HO.997) the top left hand corner of which was headed "sample letter only - not to be used". The sample letter began "Dear Doctor" and read:

"I am writing to inform you that I have decided to change the therapy of all my glaucoma patients currently on TIMOPTOL to the new longer-acting formulation of timolol, TIMOPTOL-LA (timolol maleate). New TIMOPTOL-LA brings all the established benefits of TIMOPTOL to glaucoma patients, but with the added benefit of a once-daily dosage regimen.

The cost of TIMOPTOL-LA is exactly the same as the old twice-daily formulation, TIMOPTOL, so switching to the new long-acting formulation will not increase your prescribing costs but it may improve patient compliance.

I have instructed the patient on how to use TIMOPTOL-LA correctly and also provided a patient instruction leaflet which should help facilitate the switch and ease the workload on your practice."

Spaces at the top and bottom of the letter indicated where the date etc and the ophthalmologist's signature should be placed.

The second letter was a "Dear Ophthalmologist" covering letter (ref 08-98TOTX.97.GB. 52027.SA.5c.HO.997) which reminded ophthalmologists of the benefits of Timoptol-LA and also referred to the sample GP referral letter. Ophthalmologists were told that they could use the sample letter to write to GPs, on their own hospital letterhead, informing them of the fact that patients had been switched to Timoptol-LA.

In addition to the two letters described above and provided by the complainant, the Primary Care Referral Pack contained another, alternative, referral letter suitable for when only one patient had had therapy changed to Timoptol-LA from Timoptol (ref 08-98TOTX.97.GB. 52027.LA.5c.HO. 97). The text of this alternative letter was almost identical to that above except that it did not contain the statement "New Timoptol-LA brings all the established benefits of Timoptol...". In addition to the letters there was a pad of patient instruction leaflets explaining the change in treatment and instructing patients how to use the eyedrops. The materials which constituted the Primary Care Referral Park were provided in an A4 folder which carried the same instructions as the "Dear Ophthalmologist" letter about the use of the sample GP referral letter.

All materials, except the patient instruction leaflets, carried the prescribing information for Timoptol-LA.

COMPLAINT

The complainant alleged that the "Dear Ophthalmologist" letter and the sample referral letter referring to all patients might be disguised promotion in breach of Clause 10. In addition, the complainant said that the statement regarding the cost of Timoptol-LA being the same as the old twice daily formulation was incorrect as generic timolol eye-drops were cheaper. The complainant acknowledged that Timoptol-LA was the same price as Timoptol but not the same price as the generic which was important for GPs.

RESPONSE

Merck Sharp & Dohme said that the Primary Care Referral Pack and its enclosures were clearly promotional items. No attempt was made to mislead as to the intent of the items. The pieces clearly carried the brand name Timoptol-LA and its prescribing information, and were provided in a promotional pack. The template provided was clearly marked as a "sample letter - not to be used", and referred to as such on both the pack folder and the covering letter. This template was provided as an example of the wording that might be used by an ophthalmologist when writing to GPs to inform them of the change of patients' treatment. It was left to the ophthalmologist's discretion as to the exact final wording of the letter to GPs. Merck Sharp & Dohme said that the wording of Clause 10 and the supplementary information provided in the Code were quite clear. Since it was obvious that the items were promotional pieces, and no attempt was made to present them as anything else, the company considered them to be fully in accord with Clause 10.

Merck Sharp & Dohme submitted that the template clearly referred only to switching patients established on Timoptol to Timoptol-LA, no mention was made of generic timolol or switches from it. Merck Sharp & Dohme said that the price of Timoptol was indeed the same as the price of Timoptol-LA. In any event, it was never the company's intention to compare the cost of Timoptol-LA with that of generic timolol maleate, and the company did not believe it was obliged to do so where the cost comparators were quite clear.

Merck Sharp & Dohme stated that GPs' prescribing budgets were currently debited at the NHS Drug Tariff price. The Tariff price for Timoptol, Timoptol-LA and generic timolol was in fact the same, so as far as GPs and their budgets were concerned there was no additional cost involved in a switch from Timoptol or timolol to Timoptol-LA. A copy of the relevant page from the November Tariff was provided. Merck Sharp & Dohme considered that these promotional items did not mislead directly or by implication and were therefore consistent with Clause 7.2.

Merck Sharp & Dohme explained that the pack was used by its representatives only with ophthalmologists who wished to prescribe Timoptol-LA to patients already using Timoptol. The pack was designed to help facilitate the switch from Timoptol to Timoptol-LA. As well as the written instructions provided in the pack, these ophthalmologists were briefed on the use of the pack but no other written materials were supplied to them. This took place either during one-to-one detailing or in small departmental meetings. Merck Sharp & Dohme said that it was emphasised that the letter was a template only and should be personalised when drawing up letters to GPs when medication was changed. The patient instruction leaflet was only to be used to facilitate instructing a patient in the correct use of the product after a decision to prescribe Timoptol-LA had been made. Depending on local hospital policy the representative might also have informed the pharmacy about their discussion with the ophthalmologist as a matter of courtesy.

PANEL RULING

The Panel considered that the Primary Care Referral Pack was promotional material as acknowledged by Merck Sharp & Dohme. The Panel did not accept that the "Dear Ophthalmologist" letter was disguised promotion as alleged. In the Panel's view it was a typical "Dear Doctor" letter promoting a product. No breach of Clause 10.1 of the Code was ruled in that regard.

The Panel noted that the sample GP referral letter which was the subject of complaint was relevant only in the situation where all patients were being switched from one Merck Sharp & Dohme product, Timoptol, to another, Timoptol-LA. No other companies' products were involved. In the Panel's view it was a reasonable assumption that some ophthalmologists would copy the sample letter verbatim, adding their own personal details to the top of the text and their signature to the bottom and send it to GPs. The sample letter was laid out as a "letter" which the Panel considered would encourage it to be copied unaltered.

The Panel considered that the letter was promotional. Timoptol-LA was mentioned in every sentence, each time in block capitals. The Panel noted that the letter stated that "New TIMOPTOL-LA brings all the established benefits of TIMOPTOL to glaucoma patients...". The Panel considered that this phrase, which went beyond stating some of the factual and practical issues about the therapy switch, was inappropriate for a letter intended to be sent by an ophthalmologist to a general practitioner. The Panel noted that there was no evidence to suggest that any ophthalmologist had in fact copied the letter and sent it out but considered that this was a reasonable possibility. Ophthalmologists might not fully appreciate the content of the letter. The Panel noted that the referral pack stated that the letter was provided to "...help you with the task of switching patients...". The Panel considered that including a promotional claim in what was intended for use as the text of a GP referral letter meant that the proposed letter, if used, would be disguised promotion. High standards had not been maintained. Breaches of Clauses 9.1 and 10.1 were ruled.

The Panel noted that the cost of Timoptol-LA (2.5ml) was the same price as Timoptol (5ml). Given the difference in dosage regimen, however, the daily cost of the two therapies was identical. The claim that Timoptol-LA would not increase prescribing costs compared to Timoptol was, therefore, correct. The Panel noted that, in the context of the referral pack, there was no need to consider the cost of generic timolol eye drops. No breach of Clause 7.2 was ruled.

Complaint received	**31 October 1998**
Case completed	**15 January 1998**

CASE AUTH/641/11/97

ALLERGAN v PHARMACIA & UPJOHN

Promotion of Xalatan

Allergan complained that a detail aid for Xalatan lacked the date of preparation and that the product monograph used an Allergan brand name, Propine, without its permission.

Pharmacia & Upjohn accepted that it was in breach on both points. The Panel agreed and ruled accordingly.

Allergan Ltd, a company not in membership of the ABPI, complained about the promotion of Xalatan by Pharmacia & Upjohn Ltd. The materials at issue were a detail aid and a product monograph.

COMPLAINT

Allergan alleged that the detail aid was in breach of Clause 4.7 of the Code as it did not include the date of preparation.

Allergan also alleged that the product monograph was in breach of Clause 7.10 of the Code as one of Allergan's brand names, Propine, had been used without permission.

RESPONSE

Pharmacia & Upjohn accepted that both items were in breach of the Code. The date of preparation had not been included on the detail aid and the product monograph included Allergan's brand name Propine. These were unfortunate and unintentional print errors.

PANEL RULING

The Panel ruled a breach of Clause 4.7 of the Code as the detail aid did not include the date on which the promotional material was drawn up or last revised, as acknowledged by Pharmacia & Upjohn.

The Panel also ruled a breach of Clause 7.10 of the Code as the product monograph used Propine, the brand name of one of Allergan's products, without prior consent, as acknowledged by Pharmacia & Upjohn.

Complaint received **12 November 1997**

Case completed **19 December 1997**

CODE OF PRACTICE REVIEW - FEBRUARY 1998

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PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

The Prescription Medicines Code of Practice Authority was established by The Association of the British Pharmaceutical Industry (ABPI) in 1993 to operate the Code of Practice for the Pharmaceutical Industry at arm's length from the ABPI itself.

Compliance with the Code is obligatory for ABPI member companies and, in addition, more than fifty non member companies have voluntarily agreed to comply with the Code and to accept the jurisdiction of the Authority.

The Code covers the advertising of medicines to health professionals and administrative staff and also covers information about such medicines made available to the general public.

It covers:

- journal and direct mail advertising
- the activities of representatives including detail aids and other printed material used by representatives
- the supply of samples
- the provision of inducements to prescribe, supply or buy medicines by the gift, offer or promise of any benefit or bonus, whether in money or in kind
- the provision of hospitality
- the organisation of promotional meetings
- the sponsorship of scientific and other meetings including payment of travelling and accommodation expenses in connection therewith
- the provision of information to the general public either directly or indirectly
- all other sales promotion in whatever form, such as participation in exhibitions, the use of audio-cassettes, films, records, tapes, video recordings, electronic media, interactive data systems, the Internet and the like.

Complaints submitted under the Code are considered by the Code of Practice Panel which consists of the three members of the Code of Practice Authority acting with the assistance of independent expert advisers where appropriate. Both complainants and respondents may appeal to the Code of Practice Appeal Board against rulings made by the Panel. The Code of Practice Appeal Board is chaired by an independent legally qualified Chairman, Mr Philip Cox QC, and includes independent members from outside the industry.

In each case where a breach of the Code is ruled, the company concerned must give an undertaking that the practice in question has ceased forthwith and that all possible steps have been taken to avoid a similar breach in the future. An undertaking must be accompanied by details of the action taken to implement the ruling. Additional sanctions are imposed in serious cases.

Complaints about the promotion of medicines should be sent to the Director of the Prescription Medicines Code of Practice Authority, 12 Whitehall, London SW1A 2DY (telephone 0171-930 9677 facsimile 0171-930 4554).