PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

NUMBER 20

MAY 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.

What representatives say and do

Companies are reminded that the Code of Practice applies to what representatives say and do as well as to the promotional materials which they use. They should be provided with adequate briefing material on all of the products which they are to promote in accordance with Clause 15.9 of the Code and this would be called for in the event of a complaint being received about what a representative had said.

Letters written to health professionals by representatives which mention particular products are almost certainly going to be considered promotional material and thus need to comply with the requirements of the Code, including that for certification.

Guidance can be found in the "Guidelines on company procedures relating to the Code of Practice" to be found at pages 37 and 38 in the Code of Practice booklet.

Information in abbreviated advertisements

Companies are reminded that abbreviated advertisements are restricted in content as set out in Clauses 5.4 and 5.5 of the Code and that the following information should not be included:

- product licence numbers
- references
- dosage particulars
- details of pack sizes
- cost
- quantitative particulars unless the quantitative information forms part of the licensed name of the medicine.

As indicated in the supplementary information to the Code, there may be exceptions to the above if the information provided, for example the cost of the medicine or the frequency of its dosage or its availability as a patient pack, is given as the reason why the medicine is recommended for the indication or indications referred to in the advertisement. They should not, however, otherwise be included.

Scrutiny of abbreviated advertisements by the Authority, particularly in recent issues of MIMS, shows that many contain product strengths and the like which are not acceptable. Please check your abbreviated advertisements carefully and amend as necessary. The Authority will shortly be commencing to take unacceptable advertisements up with the companies concerned.

Hospitality and meetings

A number of complaints dealt with recently by the Authority have involved meetings for UK health professionals. Cases AUTH/632/10/97 and AUTH/637/11/97 in this issue of the Review, and Cases AUTH/626/10/97 and AUTH/627/10/97 in the February 1998 issue, all related to such meetings and all were ruled in breach. Each case is judged on its own merits. Attention is drawn to Clause 19 of the Code.

In considering arrangements for meetings, factors to be taken into consideration include cost, location, educational content, the level of associated hospitality and the overall impression created by the arrangements.

Price lists including unlicensed products

Clause 1.2 of the Code exempts from its requirements trade catalogues and price lists, provided that they include no product claims, and this exemption is consistent with the requirements of The Medicines (Advertising) Regulations 1994.

The Medicines Control Agency has recently pointed out in a letter published in The Pharmaceutical Journal that an unlicensed medicine may be supplied only in response to a *bona fide* unsolicited order and that the prohibition on the advertising of such products overrides the above exemption relating to catalogues and price lists.

It is not permissible to advertise any medicine which does not have a marketing authorization and this prohibition includes listing it in catalogues and price lists.

Goodbye Emer

Emer Flynn, née O'Reilly, who had been with the Authority since its inception in 1993 and was responsible for seminars and the like, has decided not to return to work following the birth of her son and is now living once again in Ireland. The Authority thanks Emer for her help over the years and wishes her and her family well in the future.

Vicki Meyrick has taken over Emer's role as administrator and is responsible for the organisation of the Authority's seminars.

IFPMA Code procedures changed

The International Federation of Pharmaceutical Manufacturers Associations (IFPMA) has changed the procedures under which complaints under the IFPMA Code of Pharmaceutical Marketing Practices are handled. The changes will be implemented with immediate effect and primarily affect inter-company complaints. The IFPMA has issued the following "Notice to Companies".

"The IFPMA Code of Pharmaceutical Marketing Practices operated by the International Federation of Pharmaceutical Manufacturers Associations is binding on pharmaceutical companies within the membership of IFPMA, wherever they market their products throughout the world.

The primary purpose of the IFPMA Code is to provide a resource for less developed countries which have neither a strong local association with a fully operative self-regulatory Code nor effective drug legislation. Other mechanisms are available to resolve complaints arising from marketing activities in the industrialised world. With this in mind, IFPMA has revised the criteria for accepting complaints which deal with company marketing disputes.

Company vs. company complaints will no longer be accepted for processing under the IFPMA Code of Pharmaceutical Marketing Practices when they refer to alleged breaches of the Code occurring in the following countries:

- *European Union Member States*: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, United Kingdom;
- *EFTA Countries*: Switzerland, Norway, Iceland;
- *Other Industrialised Countries*: Australia, Canada, Israel, Japan, New Zealand, South Africa, United States of America;
- Other specified countries where the national association has demonstrated, to satisfaction of the IFPMA Council, the effectiveness of its self-regulatory code and operating procedures. Hong Kong falls within this category.

Companies wishing to take action against marketing practices in these countries are advised to refer the complaint to the local IFPMA Member Association or to the regulatory authority.

IFPMA will continue to handle complaints from all sources which arise out of advertising, promotion and marketing practices in the less developed countries. When such complaints are submitted by companies, however, they should be signed at the level of the CEO or corporate head of pharmaceutical business, and should indicate the steps which have been taken to resolve the problem by discussion between the companies at an appropriately senior level."

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The Authority will deal with all complaints submitted to it by IFPMA and these will either have originated from outside the industry and concern the activities of companies whose headquarters are in the United Kingdom or will be inter-company complaints involving UK companies where the alleged breaches have occurred in countries not specifically listed in the above "Notice to Companies". Such complaints will be dealt with under the IFPMA Code.

Inter-company complaints which concern activities in the UK will not be taken up by the IFPMA but will be dealt with by the Authority in the usual way under the ABPI Code of Practice for the Pharmaceutical Industry.

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:

Friday, 4 September 1998
Wednesday, 14 October 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.

GENERAL PRACTITIONER v LILLY

Conduct of a representative

A general practitioner complained about the conduct of a Lilly representative, alleging that during a discussion about antidepressant medication the representative had made many statements which the complainant considered to be somewhat exaggerated and rather misleading. In particular the representative stated that paroxetine had significant withdrawal problems. The complainant had not personally encountered such problems with it and considered that the representative had spoken of her competitor's product in a rather derogatory manner.

The Panel noted Lilly's submission that the representative had adhered closely to her detail aid. Only one page of the detail aid referred in detail to withdrawal syndrome which the Panel considered was an appropriate topic to discuss in the context of SSRIs and depression. Undue emphasis had not been given to the matter in the detail aid. Having reviewed the data provided by Lilly in relation to withdrawal treatment, the Panel considered that the statements in the detail aid were not unreasonable. There was no evidence that the representative had not adhered to the style or content of her briefing material and detail aid. The Code permitted adverse comments about competitor products if these were accurate, balanced and fair and could be substantiated. The Panel ruled that the Code had not been breached.

COMPLAINT

A general practitioner said that he had been visited by a representative from Eli Lilly & Company Limited who had discussed antidepressant medication with him. During the course of the discussion the representative had made many statements which the complainant alleged were somewhat exaggerated and rather misleading. In particular the representative stated that an antidepressant, paroxetine, had significant withdrawal problems. The complainant personally had not encountered such problems with the medicine and also considered that the representative had spoken of her competitor's product in a rather derogatory manner.

The complainant felt strongly that representatives of the pharmaceutical industry should not be spreading patently incorrect information. Not only was this damaging to the industry but it might also result in false information reaching members of the public. Some patients already perceived antidepressants to be potentially addictive without false information being fed to them.

The complainant stated that unfortunately he had not kept the business card of the representative concerned. However he hoped that some form of action could be taken in order to prevent his medical colleagues around the country being exposed to inaccurate and untrue information.

RESPONSE

Lilly noted that the complainant had alleged that the representative had made many exaggerated and misleading statements but that he was only specific with respect to the issue of paroxetine and withdrawal phenomena.

Lilly stated that its representative had taken the complainant through a Prozac detail aid (ref PZ 825). During this discussion the representative adhered closely to the content of the detail aid which covered a broad range of issues highly pertinent to the prescribing of antidepressant therapy, including:

- the fact that Prozac was the world's No. 1 prescribed antidepressant brand;
- the relative efficacy of antidepressants in depression with or without associated anxiety;
- the relative efficacy of antidepressants in improving sleep disturbance in depression, and the relative likelihood of causing daytime drowsiness;
- the dose regime and costs of various selective serotonin reuptake inhibitors (SSRIs);
- information on withdrawal phenomena with SSRIs.

At no point was undue emphasis given to paroxetine, but appropriate emphasis was given during the withdrawal section, which also provided information on the features of the syndrome reported to accompany discontinuation of SSRIs.

Lilly noted that the complainant's only specific concern was to do with the accuracy of the information given concerning withdrawal phenomena. The problem of SSRI withdrawal had been increasingly recognised over the last few years and Lilly highlighted the following areas:-

Reports to the Committee on Safety of Medicines. In 1993 the Committee on Safety of Medicines issued a report on withdrawal symptoms with paroxetine. A copy was provided. The report stated:

"We have received 78 reports of symptoms occurring on withdrawal of paroxetine, including dizziness, sweating, nausea, insomnia, tremor and confusion. Such reactions have been reported more often with paroxetine than with other SSRIs."

Young and Ashton (1996) proposed that the extended half-life of fluoxetine (Prozac) might minimise withdrawal effects. They considered that this suggestion was:

"... supported by the relatively small numbers of reports to the Committee on Safety of Medicines of withdrawal phenomena associated with fluoxetine compared with other SSRIs. We estimate that there have been approximately 13.3 such reports per million prescriptions for fluoxetine compared with 21 per million prescriptions for fluvoxamine, 35 per million for sertraline, 144 for citalopram and 238 for paroxetine."

Case reports in the literature. Barr *et al* (1994) reported 3 patients out of 6 who experienced symptoms on discontinuation of paroxetine following a 12 week trial for treatment of obsessive compulsive disorder. Symptoms occurred in these patients following cessation of

paroxetine after a 7 to 14 day taper of the dose. Frost and Lal (1995) described 3 cases of shock like sensations after discontinuation of SSRIs. Two of their patients experienced these symptoms after cessation of paroxetine and one after sertraline. Bloch *et al* (1995) described 2 cases of severe psychiatric symptoms associated with paroxetine withdrawal.

Retrospective study of clinic attenders. Coupland *et al* (1996) reported the rates of symptoms experienced in 171 outpatient clinic attendees who were supervised during antidepressant tapering and discontinuation. They defined cases as patients who experienced at least one new symptom during discontinuation. Recurrences or exacerbation of pre-existing symptoms were not sufficient to define a case. Their frequency of cases was as follows: clomipramine 30.8% (n=13); paroxetine 20% (n=50); fluvoxamine 14% (n=43); sertraline 2.2% (n=45); fluoxetine 0% (n=20).

Clinical trial data. After completion of a 12 week, double-blind study of treatment of panic disorder involving 120 patients, 34.5% of patients experienced discontinuation symptoms after abrupt cessation of paroxetine compared to 13.5% of those discontinued from placebo, Oehrberg *et al* (1995). The symptoms were rated as of moderate or mild severity. In a randomised placebo controlled study, clinically significant withdrawal symptoms did not occur after abrupt substitution of placebo for fluoxetine compared to continuing fluoxetine, Michelson *et al* (1997).

Literature review. In a review of the literature of antidepressant discontinuation, Lejoyeux and Adès (1997), it was concluded that symptoms were more common after discontinuation of a shorter acting SSRI such as paroxetine than with fluoxetine.

Pharmacological hypothesis about the symptoms. Haddad (1997) proposed reasons for the differences in incidence of discontinuation reactions amongst SSRIs:

"Fluoxetine (low risk of discontinuation reactions) has the longest half-life of the SSRIs, while paroxetine (high risk of discontinuation reactions) has one of the shortest half-lives."

"Pharmacokinetic factors, including short half-life, absence of active metabolites and autoinhibition may contribute to the high rate of discontinuation symptoms that are seen with paroxetine. These factors may also contribute to the severity of discontinuation phenomena."

Definition of a syndrome. Schatzberg *et al* (1997) proposed a definition of a syndrome of SSRI discontinuation. The hallmark features were:

"Not attribute to other causes

Emergent upon abrupt discontinuation, intermittent non-compliance (eg missed doses, drug holidays) and less frequently with dose reduction

Generally mild and short-lived

Self-limiting and can be distressing

Rapidly reversed by the reintroduction of the original medication or the substitution of one that is pharmacologically similar

Minimised by slow tapering or using a drug with an extended half-life"

Management. Rosenbaum and Zajecka (1997) recommended the following strategies to manage discontinuation events:

"Reassure the patient that the symptoms are likely to be short-lived and mild

For acute symptoms, reinstitute the dosage and slow the rate of taper

Gradually taper all serotonin reuptake inhibitors except fluoxetine

Treat with agent with an extended half-life, eg fluoxetine"

Information to doctors and patients. Lilly noted that the complainant had expressed concerns about the effect of information about antidepressant withdrawal, particularly with regard to the effect on the public. Young and Currie (1997) reported the results of a survey of physicians' knowledge of antidepressant withdrawal effects. They suggested that:

"routinely educating patients about the possibility of antidepressant discontinuation symptoms may be justified since patients often become noncompliant and abruptly stop taking their medication"

and

"physicians must become comfortable with implementing appropriate tapering schedules when discontinuing the shorter acting SSRIs such as paroxetine, venlafaxine and fluvoxamine. Fluoxetine, on the other hand, which has an extended half-life, is much less likely to cause discontinuation-emergent symptoms and, for the most part, tapering is not required for fluoxetine."

Lilly stated that though withdrawal symptoms might occur on cessation of antidepressants, these medicines did not elicit other symptoms of a dependence syndrome. It submitted that education of doctors and patients about withdrawal phenomena was important in helping to prevent such experiences. Preventing such symptoms would be important in avoiding the association of antidepressants with problems of addiction in the minds of patients.

In summary, Lilly understood that the content of the complainant's discussion with its representative was restricted to the content of the Prozac detail aid. The complainant only mentioned the withdrawal symptoms related to discontinuation of paroxetine specifically. It did not accept that the claims made in this regard were exaggerated or misleading, or "patently incorrect".

Lilly stated that withdrawal phenomena following discontinuation from SSRI treatment, whether or not the complainant had encountered them, were a significant issue in the treatment of depression. It believed it would be misleading either not to mention withdrawal phenomena at all, or to fail to mention the particular association of paroxetine with such events.

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Following receipt of the response from Lilly, the Panel requested more details about what was actually said by the representative and the complainant.

FURTHER RESPONSE FROM LILLY

Lilly stated that the representative concerned remembered this meeting very clearly. It occurred after a lunchtime meeting at the practice, during which she had taken a group of doctors from the practice through the detail aid. The complainant arrived towards the end of the meeting, and the representative, apologising to the doctors already present, went through the detail aid again for the complainant's benefit. The complainant stated that he preferred paroxetine for his depressed patients, and subsequent discussion therefore focused on the differences between the two products, adhering closely to the briefing material. The issue of discontinuation syndrome came up, and it was clear that the complainant had not encountered this problem. Since the syndrome often went unrecognised, the representative described the symptoms often associated with the syndrome, and the relative risks of the syndrome occurring with Prozac and paroxetine. She remembered the discussion concluding with the complainant stating that she had made a strong argument for him to consider Prozac for some of his patients. Her overall impression of the meeting was that it was cordial and that the complainant at no time seemed annoyed or indignant. The representative's story was given some credibility by the opinion of her manager, who stated that her style with customers was one of sticking closely to the material provided. She was not known for exaggeration.

Lilly stated that why the complainant should, possibly after some reflection, feel quite so aggrieved following this meeting was not clear. The detail aid was broad and did not focus unduly on paroxetine or discontinuation syndrome. The briefing material was factual in content and not exaggerated or derogatory in style. According to its representative the meeting closely followed this material.

It was possible that the complainant misinterpreted the information he was given on the frequency of under-recognition of discontinuation syndrome as a criticism of his clinical judgement or diagnostic skills. If so, this was not intended. As indicated in previous correspondence, the association of paroxetine with this syndrome was not "patently incorrect", at least according to the CSM and the majority of published research.

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Following receipt of the further information from Lilly, it was decided that both of its responses should be sent to the complainant for comment. It was thought appropriate to take this course of action as it had on occasion been found helpful in cases where it was difficult to be certain as to what had been said. There was a two month delay in receiving the complainant's further comments.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant agreed that he entered the meeting late due to pressure of work and that the meeting was entirely cordial. He also accepted that the issue of the discontinuation syndrome was discussed and that he had made it clear that despite considerable use he had not experienced this problem.

The complainant considered that any representative should stress the positive aspects of his or her medication rather than the negative aspects of anybody else's product. The complainant pointed out that he had been medically qualified for well over twenty years and it was the first time that he had ever considered it necessary to write to a pharmaceutical company with reference to one of its representatives.

The complainant suspected that the Lilly representative was staying within her basic remit but the overall argument as to the advantages and disadvantages of the two products was inappropriately stressed.

The complainant still considered that paroxetine was an excellent medicine and he would continue to use it.

PANEL RULING

The Panel noted the submission that the representative had adhered closely to the content of the detail aid. It noted only one page of the detail aid referred to withdrawal syndrome in detail. The other pages referred to the efficacy and ease of use of Prozac in the management of depression. In the Panel's view, withdrawal syndrome was an appropriate topic to discuss in the context of SSRIs and depression. The Panel did not consider that the detail aid gave undue emphasis to the matter.

The Panel examined the data provided by Lilly. Young & Ashton (1996) stated that the slow elimination of fluoxetine might minimise withdrawal effects but prolong risk of drug interactions. Using reports to the CSM of withdrawal phenomena associated with fluoxetine, Young & Ashton (1996) estimated 13.3 cases of withdrawal phenomena per million prescriptions for fluoxetine compared with 238 per million prescriptions for paroxetine. Coupland *et al* (1996) examined SSRI withdrawal in 171 patients and found that when patients with at least one qualitatively new symptom were defined as cases, the symptoms of withdrawal occurred significantly more frequently in patients who had been treated either with one of the shorter half-life SSRIs, fluvoxamine or paroxetine (17.2%) or with clomipramine (30.8%) than in patients taking one of the SSRIs with longer half-life metabolites, such as fluoxetine (1.5%). In addition the Panel noted the paper by Haddad (1997), which concluded by noting that the general consensus from published case reports, databases and reactions which had been spontaneously reported to national monitoring bureaux, was that rates of SSRI discontinuation reactions were highest for paroxetine, lowest for fluoxetine and intermediate for the other SSRIs. The Panel also noted that the Seroxat data sheet recommended that paroxetine be withdrawn gradually (ref ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1996-97).

The Panel considered that the statements in the detail aid relating to withdrawal of treatment which highlighted the differences between Prozac and paroxetine were not unreasonable given the data. There was no evidence that the representative had not adhered to the style or content of either the briefing material or the detail aid although the Panel recognised that in an interactive discussion it was difficult to know what had been said.

The Panel noted the complainant's comment that representatives should stress the positive aspects of their

product and not the negative aspect of anyone else's. 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.

Given the content of the detail aid and the briefing material the Panel did not consider that the representative had presented unbalanced or misleading data, nor had she been disparaging about her competitor. No breach of the Code was ruled.

Complaint received **28 July 1997**

Case completed **2 February 1998**

CASE AUTH/603/8/97 *NO BREACH OF THE CODE*

PATIENT v BOEHRINGER INGELHEIM

Market research interview

A married couple complained about the unprofessional way a market research company had conducted a survey on a new inhaler on behalf of Boehringer Ingelheim. The mother of one of the complainants had been interviewed. She had been pushed into the interview and had been told that the product she was now using was inferior to that she had previously taken. Her doctor was a fundholder and was prescribing cheaper inferior medicines so as to make a profit. As a result of what had been said, and in addition to her previous conditions, she was now worried sick and suffering from anxiety, stress and depression.

The Panel observed that the only requirement in the Code relating to market research was that it must not be disguised sales promotion. The Panel noted that Boehringer Ingelheim had stated that all those taking part had volunteered to do so and that more people than needed had come forward. There was no question of anyone being forced to take part. The market research was designed to elicit views on the ease of use and mechanics of inhalers. The relative merits of inhalers were not discussed or challenged. The Panel considered that the market research was not disguised promotion and ruled no breach of the Code.

The complainants appealed the Panel's decision saying that the version of events given by Boehringer Ingelheim to the Panel was inaccurate and that the information on medication etc complained of had been given in conversation prior to the actual interview. Boehringer Ingelheim said that no reason had been given by the complainants to dispute the Panel's ruling but considered that the allegations needed action in order to protect the reputation of the industry. The complainants' insistence on anonymity prevented detailed investigation.

When the Appeal Board first considered the matter it decided that further information was needed from both parties. It was agreed that the Chairman should write to the complainants and ask if the mother's name and the name of the market researcher could be revealed to Boehringer Ingelheim. If not, then would they reveal the venue at which the interview had taken place?

The complainants asked that the matter be brought to an end, however, and did not provide further information. Following receipt of a letter from Boehringer Ingelheim, which had been passed on to them by the Authority, they were satisfied that the matter would be looked into in more depth and that the company was taking the matter seriously.

The Constitution and Procedure did not provide for the withdrawal of an appeal at this late stage but the Appeal Board considered that it would be wrong to hear the appeal and decided to adjourn it *sine die*. This meant that the case was adjourned and in practice would not be reopened. The Panel's ruling of no breach would stand.

COMPLAINT

A patient's son and his wife complained about the unprofessional way a market research company had conducted a survey on a new inhaler on behalf of Boehringer Ingelheim Limited. The market research company had interviewed the son's mother who already had arthritis, bad heart, cardiac asthma, hardening of the arteries, water retention and insomnia and, as a result of the interview, now had "anxiety and stress". The complainants listed a number of key issues.

1 The mother was not keen to take part. She was hounded and forced into it. The interviewer would not take no for an answer and was very pushy.

2 She was told by the interviewer that the product she was taking, salbutamol, was inferior to Ventolin, which she had previously taken. That her doctor, being a fundholder, was now prescribing generic products which were much cheaper, inferior medicines, not exactly the same, to make as much profit as he could.

3 When asked had anybody shown her how to use her salbutamol (she said 'no'), and had she ever had any trouble with it, she was then told that her doctor or the nurse should have. They were not doing their jobs properly and inadequate puffs or not taking it correctly, especially during an attack, could kill her.

4 She was told that was why they had brought out these new powder inhalers, because you did not have to swallow it correctly and did not need any breath. Just press and the correct dose goes into your mouth.

5 She was also told that a lot of doctors were now picking and choosing their patients and those who were severely ill or on a lot of medication or needed expensive operations were being asked to leave the surgery. Apparently they could do this and did not need to give an explanation.

The complainants said that as a result of this their mother was worried sick, suffering from anxiety, stress and depression. The complainants said that their mother would not listen to anything they said. They kept arguing as she wanted to leave the doctor's surgery after being

there for 25 years. The mother told them that she had now lost all faith in him. She had stopped taking her salbutamol saying it was not doing her any good, not giving her relief anymore (she was however still taking her preventative one), and wished to change to a new doctor so that she could get a powder inhaler.

The complainants said that they had suggested that their mother went to her own doctor and explain how she felt but she refused to discuss it. Her reply was "The girl from Boehringer knows what she is talking about not you, that is her job, they are a pharmaceutical company, they make the medicines so they should know all about them".

The complainants said that the whole family was divided and under a great deal of strain owing to the actions of this pharmaceutical company and if anything happened to their mother due to this stress they would be holding them responsible. That was why the couple were writing to the Authority, so there was a registered record of their complaint. They were not after an apology, as nothing could reverse the problems that this incident had caused.

They had been asked how they knew it was Boehringer Ingelheim which was involved. The interviewer had told them. Their mother would not do the interview unless she knew whom it was for. The daughter-in-law was there when she was told; it was for a German company called Boehringer Ingelheim which specialised in the asthma market. The complainants said that they were not supposed to be told this. It was supposed to be confidential.

RESPONSE

Boehringer Ingelheim stated that the research was commissioned by its corporate market research department through an organisation in Switzerland which engaged an agency in the UK to perform the research. Patients were invited to participate with the approval of their general practitioner who was to recommend patients fitting in with a predetermined clinical profile. A letter was given to each of the patients so recommended. Only patients responding to the letter and agreeing to attend for the purposes of the market research were interviewed. The letter clearly requested cooperation, offered reasonable compensation for the patient's time and provided normal guarantees to the patient in respect of the research. In addition, by way of preliminary information, patients were asked to record duration of treatment and to name their medicine and delivery device. Age, name and address were also requested so as to meet the clinical sample requirements and to allow contact with the patient.

Boehringer Ingelheim said that more patients volunteered than were needed for the survey. The interviews were conducted at Slough, Newnham-on-Severn and Swansea and involved a total of 42 patients all of whom had attended voluntarily following return of the preliminary questionnaire. The interviews were conducted by three trained interviewers seeing the patients by appointment and all interviews were recorded on videotape and audiotape (a written and video copy of each interview was provided by Boehringer Ingelheim).

Boehringer Ingelheim had contacted the agency and had ascertained that no interviewer experienced reluctance, withdrawal of cooperation or other difficulties with any of the patients and neither did any of the interviews suggest any discord or evidence of patient distress at or during the procedure. In fact the complaint and the allegations came as a total surprise to the agency which could confirm that to its knowledge no such events as described by the complainant occurred.

Boehringer Ingelheim supplied a copy of the interview and procedures. Boehringer Ingelheim submitted that examination of this document showed that the research concerned devices and sought information on products merely to establish the nature of the device or delivery system being used. There was no research conducted upon the medicine at all and thus no opportunity to discuss the efficacy of generic salbutamol as opposed to Ventolin.

In view of the above Boehringer Ingelheim submitted that the events described and alleged by the complainant did not occur and that the market research performed was correctly and properly conducted without causing distress or offence, ie not in breach of Clause 9.1. Further the company confirmed that no form of medicinal product or approved device was being promoted overtly or covertly, ie the market research was a genuine investigation and not in breach of Clause 10.2. For these reasons Boehringer Ingelheim contended that no breach of Clause 2 could have occurred.

PANEL RULING

The Panel noted that the only requirement relating to market research was Clause 10.2 of the Code which stated that market research activities, post-marketing surveillance studies, clinical assessments and the like must not be disguised promotion.

The Panel noted that all those taking part in the market research had volunteered to do so and that according to Boehringer Ingelheim more people than were needed had come forward. There appeared to be no question of anyone being forced to take part. The Panel noted that the market research interview was designed to elicit views on the ease of use and mechanics of inhalers. The relative merits or efficacy of any inhaler were not discussed or challenged. Although those being interviewed were asked which inhalers they currently used the interview did not include any questions about any specific inhaler. The Panel considered that the market research was not disguised promotion and therefore no breach of Clause 10.2 of the Code was ruled.

During its consideration of this case the Panel noted that the "Guidelines on Pharmaceutical Market Research Practice" issued by the British Pharmaceutical Market Research Group and the ABPI gave advice on the conduct of market research. The Panel decided that the complainants should be provided with a copy of the Guidelines and advised that the matter could be referred to the committee that dealt with matters relating to the Guidelines.

APPEAL BY THE COMPLAINANTS

The patient's son said that he was rather surprised to read the Authority's letter as nothing in it had happened as stated. His mother was recruited at her home, by the

interviewer. She never filled in a form that was left at a doctor's and the only reason she said yes was because the interviewer who had pressured her to come and do the interview was a friend of a friend that they knew, and therefore she felt obliged to help.

Boehringer Ingelheim had stated that "patients were invited to participate with the approval of their general practitioner who was to recommend patients fitting with a predetermined clinical profile". This was a load of lies.

The complainants were told by the interviewer that she was desperately short in numbers and especially of their mother's age, which she needed badly, and not to let her down. The fact that the mother was pressured into doing the interview was not the main issue, the complainants realised this was because the person knew their friend and put their mother under an obligation. She was only called on and pushed into doing this the day before the event. Therefore how could she have filled in a form and sent it back and received a letter etc? It was all a total load of rubbish. She was given an invitation the night before, which she brought along and handed in on arriving.

It was what the other interviewer said in running down salbutamol and therefore taking all their mother's confidence away from the product and her doctor, which was giving the complainants concern for her health and causing them distress (their mother had mistakenly thought that she was a representative from Boehringer Ingelheim). If she had not gone along to the interview this would not have happened.

The complainants were so concerned at the time that they rang salbutamol's makers to ask them if it was true what had been said about their product being a cheaper, less stronger inferior version of Ventolin. It was the company that gave the complainants the Authority's address and suggested them making a complaint as what was said was unethical and wrong. The company was wonderful and gave them a personal number should their mother require help or need to be reassured in any way. The gentleman the son spoke to gave them the reassurance and help that he did not expect to receive.

In the letter from the agency, it said no medicines etc were discussed, yet in the recruitment questionnaire page 1 that the Authority sent, it asked what medicines were you using, and on page 4 asked whether you initially had any difficulty using your inhaler.

The son added that he did not say that the advice on being given a cheaper brand of her medication etc and the conversation about which medicines it would be better for her to use occurred during the interview; those remarks were all made in the conversation prior to that whilst waiting to be interviewed and in a general form of discussion, when talking about what she was on, and what was going to be asked during the interview etc. Therefore this part would not be on videotape. As a matter of fact, their mother was not aware that it was going to be taped until that day and that caused her some concern as well as she would not have gone if she had known.

The fact was that the interviewers were working on behalf Boehringer Ingelheim, a large pharmaceutical company. Therefore it was Boehringer Ingelheim that must be held responsible for these actions and anything that happened as a result of irresponsible advice and behaviour given.

If they were being truthful in stating they had too many respondents why was their mother pushed into coming at the last minute and why was another friend of hers, who did not even suffer from asthma, asked to come along and pretend she used a Turbohaler (she did this very reluctantly too)? She was even given a Turbohaler to take along to the interview in case she was asked to show what she used. All a pack of lies. Whenever the complainants heard or saw market research results etc they would say "what a load of rubbish".

COMMENTS FROM BOEHRINGER INGELHEIM

Boehringer Ingelheim's basic response was that the complainants had not given any reason for appealing against the ruling on Clause 10.2 of the Code which dealt specifically with market research being disguised promotion, but rather repeated and enlarged on the alleged events surrounding the market research activities sponsored by Boehringer Ingelheim.

The Panel, having considered the documentation provided by the company and the conduct of the market research, had concluded that it was not disguised promotion. In the absence of any evidence that this market research was in any way promoting the use of a Boehringer Ingelheim product, the conclusion had to be that it could not have been disguised promotion and therefore could not have been in breach of Clause 10.2 of the Code.

The Panel, in its ruling, noted that the only requirement of the Code relating to market research was Clause 10.2. Boehringer Ingelheim therefore concluded that the Appeal Board should uphold the original ruling of the Panel that there had been no breach of the Code.

However, the allegations in this case required some action in order to protect the reputation of the industry. The facts of the case could neither be confirmed nor refuted and the complainants' insistence on anonymity made full investigation very difficult. There was an appearance of truth in the allegations and Boehringer Ingelheim proposed that the matter be referred to the British Pharmaceutical Market Research Group (BPMRG) in that there might have been contravention of Clauses 2.2 and 2.3 of the Guidelines on Pharmaceutical Market Research Practice issued jointly by the BPMRG and the ABPI.

FURTHER COMMENTS FROM THE COMPLAINANTS

No further comments were received.

INITIAL APPEAL BOARD CONSIDERATION

The Appeal Board gave initial consideration to this case and decided that it needed more information from both the complainants and the respondent before it could make a ruling.

The Appeal Board was very concerned that a patient had been so distressed by market research carried out by a market research agency on behalf of a pharmaceutical company. The allegation that, prior to an interview, a market researcher had indirectly promoted one product by disparaging another was a serious one and needed to

be thoroughly investigated. The Appeal Board noted the complainants' insistence that their mother's identity should be withheld from Boehringer Ingelheim. Boehringer Ingelheim did not even know at which of the three venues, Slough, Newnham-on-Severn or Swansea, the interview in question had been conducted.

The Appeal Board decided that the complainants should be asked to reveal the name of their mother. This information would not be passed to Boehringer Ingelheim. The complainants should also be asked to reveal the name of the market researcher so that the information could be passed to Boehringer Ingelheim to enable the company to fully investigate the circumstances. If the complainants were not prepared to give the name of the market researcher, then they should be asked to identify the venue at which the interview took place and this would be passed to Boehringer Ingelheim. The Appeal Board suggested that the Chairman should write to the complainants.

The Appeal Board considered that it also required more information from Boehringer Ingelheim. The company should be asked to supply the names of all the interviewers and corresponding interviewees from each of the three centres. The Appeal Board noted that coded completed questionnaires had been supplied to the Authority. The Appeal Board requested that Boehringer Ingelheim be asked to provide information so that the coding could be broken in order that the complainants' mother's form could be identified.

FURTHER CONSIDERATION BY THE APPEAL BOARD

The Appeal Board noted that at its meeting in December it had decided to request further information from both the complainant and the company in order to deal with the matter. The Chairman had written to the complainants requesting further information. The complainants advised by telephone on 8 January 1998 that they wished to bring an end to the matter. They had written to the Authority on 14 December 1997 but their letter had not been received. A copy of it was received on 13 January 1998.

The Appeal Board was reminded that Paragraph 14.2 of the Constitution and Procedure for the Prescription Medicines Code of Practice Authority stated that notice of appeal might be withdrawn by a complainant with the consent of the respondent company up until such time as the respondent company's comments on the reasons for the appeal had been received by the Authority but not thereafter. It was not therefore possible for the appeal to be withdrawn.

The Appeal Board noted that the circumstances in this case were unusual. The complainants had requested that the matter be brought to an end and had not provided the further information requested by it. The Appeal Board noted that the letter from the complainants stated that they were satisfied that the matter would be looked into in more depth and dealt with and that everything that could be done had been done. The complainants had received a letter from the medical director of Boehringer Ingelheim which the Authority had passed on to them and they appreciated that the company was taking the matter seriously.

The Appeal Board decided that in the circumstances it would be wrong to hear the appeal. The Appeal Board decided to adjourn the matter *sine die* (without a day). This meant that the case was adjourned and in practice would not be reopened. The Panel's ruling of no breach would stand.

It was considered that it would be helpful if the case report was circulated, for information only, to the group that dealt with the ABPI/BPMRG Guidelines on Pharmaceutical Market Research Practice and to remind that Group that attention needed to be paid to what happened before and after, as well as during, a market research interview.

Complaint received	**18 August 1997**
Case adjourned *sine die*	**29 January 1998**

CASE AUTH/611/9/97

PROCTER & GAMBLE v MERCK SHARP & DOHME

Bandolier conference report

Procter & Gamble complained about an addendum to the "Report of the 3rd Bandolier Conference - Osteoporosis", the data analysis for which was attributed to Merck Sharp & Dohme. This was a cost-effectiveness comparison of Procter & Gamble's product Didronel PMO (cyclical etidronate) with Merck Sharp & Dohme's product Fosamax (alendronate). It was alleged that the cost effectiveness comparisons had been presented in a way which was incomplete and misleading. The addendum contained "numbers needed to treat" (NNT) data and the data to calculate cost per fracture had been taken from two particular studies, the Harris study and Merck Sharp & Dohme's Fracture Intervention Trial (FIT) data, despite more favourable efficacy data being available and published for Didronel PMO in the Storm study. Procter & Gamble further alleged that the involvement which Merck Sharp & Dohme had had in the organisation of the conference and the subsequent report was not clearly highlighted. The addendum had gone to all who attended the conference and was in breach because no prescribing information had been provided.

The Panel noted that the FIT study had included 1,946 patients and the Harris 3 year data 289 patients whereas the Storm data had included only 37 patients. The Panel considered that given the choice between the two 3 year studies for etidronate (Harris and Storm) it was not unreasonable to use the data from the larger study (Harris) in the addendum, which stated that one of the criteria for choosing a study was that it had to have at least 100 patients involved. The Panel noted that when comparing the results from different studies it was difficult to ensure that the studies were directly comparable. Given the choice of data available, the Panel considered that it was not unreasonable to use the data from the two largest studies. No breach of the Code was ruled.

Upon appeal by Procter & Gamble the Appeal Board considered that the choice of papers by Merck Sharp & Dohme was not unreasonable but questioned the basis of the calculations presented in the addendum. It was far from clear how the cost per fracture had been calculated. The Appeal Board noted that the NNT for etidronate was marked non-significant. The Appeal Board noted that the addendum had been distributed more widely than just to those who attended the conference. It was on the Bandolier website and Merck Sharp & Dohme's representatives had been provided with it. In the Appeal Board's view, some readers would assume that a full economic evaluation had been undertaken and this was not so. There was insufficient explanation of the data. A breach of the Code was ruled.

The Panel noted that no acknowledgement of Merck Sharp & Dohme's role as a joint sponsor of the conference appeared in the conference report and ruled a breach in that regard. A breach was also ruled in respect of the failure to include prescribing information in the addendum, which the Panel considered constituted promotional material for Fosamax.

Procter & Gamble Pharmaceuticals UK Ltd complained about an addendum which had been printed on the back page of the "Report of the 3rd Bandolier Conference - Osteoporosis". The addendum contained "numbers needed to treat" (NNT) data and was a cost-effectiveness comparison of Procter & Gamble's product, Didronel PMO (cyclical etidronate) with Merck Sharp & Dohme Limited's product, alendronate. Data taken to calculate cost per fracture saved had been taken from a study by Harris (cyclical etidronate) and the FIT (Fracture Intervention Trial) study (alendronate). The headings to the three charts given in the addendum were each followed by an asterisk. The explanation for the asterisk, details of the criteria for review, appeared at the foot of the page. The addendum stated that the data analysis was attributed to Merck Sharp & Dohme. Proctor & Gamble understood that Merck Sharp & Dohme had supplied the data to the conference organisers following a question from one member of the audience. The conference took place in January 1997 and the meeting report was issued later in the year to all attending delegates. Merck Sharp & Dohme stated that Bandolier was an independent evidence-based monthly journal based at the Churchill Hospital, Oxford and published for the NHS R&D Directorate.

COMPLAINT

Procter & Gamble alleged that the cost effectiveness comparison in the addendum had been presented in a way which was incomplete and misleading in breach of Clause 7.2 of the Code.

Procter & Gamble noted that only data from the Harris study (1993) had been used for the purposes of a cost comparison with Merck Sharp & Dohme's FIT data, despite more favourable efficacy data being available and published for Didronel PMO (eg Storm *et al* (1996)).

Procter & Gamble said that Merck Sharp & Dohme claimed that Harris was the only study which fulfilled the strict scientific criteria detailed for comparison purposes (outlined as a study design of appropriate size, prospective, double blind, randomised, placebo controlled, of similar duration and published in a peer reviewed journal). Based on these criteria, Procter & Gamble considered that the 0-3 year results from the more recent peer reviewed publication by Storm (1996), were equally as appropriate as the Harris (1993) data for the cost effectiveness comparison made by Merck Sharp & Dohme.

Procter & Gamble said that under the veil of scientific rigour, Merck Sharp & Dohme claimed that the Storm study might not be relevant for comparison because it was an inappropriate study size and the patients in the Storm study had a higher risk of osteoporosis compared to those patients in the FIT study. Neither of these alleged reasons to exclude the Storm data were supported by the references cited in Merck Sharp & Dohme's correspondence to Procter & Gamble. Indeed, there was no guidance within the literature quoted by Merck Sharp & Dohme, with regard to what was an appropriate study size, when making comparisons. In addition, disease risk was not an applicable exclusion criteria to adopt in cost

effectiveness models, as it was the treatment effect (the difference between active and placebo) that provided the basis of the cost analysis (ie in this case NNT - numbers needed to treat). The implementation of such arbitrary exclusion criteria meant that more favourable data for Didronel PMO had been purposefully omitted from the analysis and as such, made the current comparison misleading and the conclusions inappropriate.

The data provided in the addendum showed that the cost per fracture saved was £13,701 for alendronate (taken from the FIT vertebral data) and £15,810 for cyclical etidronate (taken from the Harris vertebral data 0-3 years). Procter & Gamble submitted that if more favourable efficacy data for cyclical etidronate had been used then the cost per fracture saved would have been less. The Harris data (vertebral, 0-2 years) would have given a cost of £9,362 while the Storm data (all vertebral, 0-3 years) would have given a cost of £7,391. (In all calculations Didronel PMO cost 45p/day and alendronate 92p/day).

In addition Procter & Gamble stated that the involvement which Merck Sharp & Dohme and/or its communication agency had had in the organisation of this educational meeting and subsequent report was not clearly highlighted. Breaches of Clauses 9.9 and 19.3 of the Code were alleged.

Procter & Gamble pointed out that the Merck Sharp & Dohme addendum was produced as a result of only one audience member asking a question. However, the data had been issued to all attendees unsolicited which was in breach of Clause 11.1 of the Code as no prescribing information etc had been provided.

Procter & Gamble requested that no further use was made of the conference report and addendum. Given that this inaccurate information had been widely disseminated, including to those persons responsible for undertaking hospital formulary decisions, the company considered that a clarification statement from Merck Sharp & Dohme should be sent to those persons who received the analysis stating that the data relating to Didronel PMO were not correct and that accordingly the comparison sought to be made between the products was inaccurate and should not be relied upon.

RESPONSE

Merck Sharp & Dohme said that it did not use the two year vertebral data from Harris (as quoted by Procter & Gamble) because the study was of a shorter duration than the three year FIT study. This view was supported by Laupacis *et al* who advised that "extrapolating data from one interval to another is always dangerous and can only be done with confidence when the benefit and harm are known to be constant." It was apparent from the data quoted by Procter & Gamble that the risk reduction between the two and three year points in the Harris study changed considerably (from 45% to two years to 18% at three years) and lent further credence to this argument.

Merck Sharp & Dohme said that it did not use the three year data re-quoted by Storm in 1996 for the following reasons:

1 The number of evaluable patients were extremely small. Only 37 patients were evaluable at the three year time point, compared to 289 at three years in Harris and 1946 in the FIT study. The accuracy of NNT derived from the sample in a study as an estimate of the NNT applying to the whole population would increase with the size of the sample as reflected by the 95% confidence limits. For Harris the 95% confidence intervals for NNT for vertebral fracture were 10 - ∞ (convention dictated infinity rather than a negative number for the upper limit with non-significant data), and for FIT 95% confidence intervals for NNT for any fracture were 9-24. Sample size might also account for the large difference in derived NNT between the three year data for Storm and Harris (15 versus 32 respectively). The limits for FIT were much smaller reflecting its large size in comparison to Harris. In addition, the re-analysis of number of patients with fractures over 3 years that Storm performed in 1996 was calculated only for those patients who continued on open label therapy in years 4-5. This was thus a post hoc analysis which was potentially open to bias.

2 Merck Sharp & Dohme also considered that the patient group recruited into the original Storm study published in 1990 had a much higher risk of subsequent fracture than did those in either the FIT study or the Harris study and were thus not strictly comparable. This was because patients that had suffered a vertebral fracture were five times more likely to suffer a subsequent vertebral fracture than patients that had not previously sustained a fracture (Ross *et al*). The proportion of patients with fracture in the placebo groups over three years was much higher for the Storm study published in 1996 (85%) than for the FIT study (15%) and Harris (17%). A small study was more likely to be unduly influenced by fractures in a small number of patients by chance. Larger studies were less so, as indicated by tighter confidence limits. A method had been developed to compensate for the differences in baseline fracture risk when calculating NNTs. However this method depended upon the assumption of a constant relative risk reduction by the treatment at varying baseline risks. The data from the Harris and Storm studies did not support this; differences in baseline risk had been discussed above, and the relative risk reduction for vertebral fractures in Harris was 18% and in Storm 31%. Therefore, the basic assumption for the method was not met, and it could not be used.

In explaining its involvement with the project Merck Sharp & Dohme said that it had approached Bandolier via a communications company to discuss a programme for a conference on osteoporosis that would be sponsored by the company. Conference speakers were approached by either the communications company or by Bandolier to assess their interest in participating in this meeting. Speaker briefs were subsequently approved and distributed by Bandolier.

Merck Sharp & Dohme said that one of the editors of Bandolier chaired the conference and in his opening remarks to delegates specifically thanked the two sponsors of the meeting, Merck Sharp & Dohme and the Research and Development Division of the Department of Health. All speakers were informed of the sponsorship before the meeting. The role of Merck Sharp & Dohme as joint sponsor was also apparent from the presence of an Merck Sharp & Dohme promotional stand distributing company sponsored material. Merck Sharp & Dohme was the only pharmaceutical company represented at the

meeting.

Merck Sharp & Dohme said that the meeting report was drafted by a freelance writer supported by the company. Both Merck Sharp & Dohme and Bandolier provided input on the draft, which was then circulated to each speaker. Bandolier then made final changes based on any speaker comments.

Merck Sharp & Dohme said that a discussion point at the conference following Professor David Hosking's presentation on bisphosphonates had been how many patients would be needed to prevent a fracture with alendronate. Professor Hosking replied that the Fracture Intervention trialists had not published any such data and that he did not know the answer. Merck Sharp & Dohme subsequently discussed with Bandolier the appropriateness of including the NNT data as an addendum to the report. This was agreed with the editorial board at Bandolier. Merck Sharp & Dohme supplied a one page addendum, which was added to the initial draft of the conference report and submitted to Bandolier. Bandolier finalised the report and then issued it to all conference delegates and speakers. The report was not sent in an unsolicited fashion as Procter & Gamble had claimed.

Merck Sharp & Dohme said that the report and addendum had not been used as a promotional piece. The salesforce were provided with one copy of the report and addendum for reference, so that they were aware of the contents if questions or comments were raised about the report by a customer.

PANEL RULING

The Panel noted that the addendum to the Bandolier conference report compared the cost per fracture saved with alendronate with the cost per fracture saved with cyclical etidronate. Data for the comparison had been taken from the FIT for alendronate and from a 3 year study by Harris for etidronate. According to the addendum it cost more to save a fracture with etidronate than with alendronate. The Panel noted Procter & Gamble's contention that the cost per fracture saved with cyclical etidronate would have been less than with alendronate if data from Harris (0-2 years) or data from Storm (0-3 years) had been used.

The Panel noted that the addendum was an analysis of data from two entirely different studies. The criteria for choosing which studies to compare were given in the addendum as studies which were randomised double-blind trials versus placebo which included more than 100 patients and which showed a statistically significant result. The Panel noted that the two studies used by Merck Sharp & Dohme were of similar duration, the FIT study lasted for 2.9 years and the Harris study was based on aggregate data for years 0-3. The Panel considered that it was not unreasonable to compare only studies of similar length, particularly where there was evidence that fracture rates differed over different time periods.

The Panel noted that FIT had included 1946 patients and the Harris 3 year data included 289 patients. The Storm (0-3 year) data had included only 37 patients. The Panel considered that given the choice between the two 3 year studies for etidronate (Harris or Storm) it was reasonable to use the data from the large study (Harris) in the addendum. The addendum clearly stated that one of the criteria for choosing a study was that it had to have at least 100 patients involved. The Panel acknowledged that the criteria excluded the use of the Storm data but did not consider this unreasonable.

The Panel noted that when comparing the results from different studies it was difficult to ensure that the studies were directly comparable. The Panel considered that, given the choice of data available, it was not unreasonable to take data from the two largest 3 year studies, ie FIT and Harris (0-3 years). No breach of Clause 7.2 was ruled.

The Panel noted the requirements of Clause 19.3 of the Code which stated that "When meetings are sponsored by pharmaceutical companies, the fact must be disclosed in the papers relating to the meetings and in any published proceedings". The Panel noted that while Merck Sharp & Dohme were joint sponsors of the Bandolier conference no acknowledgement of that fact appeared on the conference report. The addendum stated that the data analysis was by Merck Sharp & Dohme. This was not sufficient. The Panel ruled a breach of Clause 19.3. The Panel considered that the lack of acknowledgement of sponsorship of the meeting was covered by its ruling of a breach of Clause 19.3 of the Code. It therefore ruled no breach of Clause 9.9.

The Panel noted that the addendum had been produced as a consequence of a question posed to a speaker at the conference which, through lack of data at the time, the speaker had been unable to answer. The question had been a discussion point at the conference and as such the answer would be of interest to all delegates.

With regard to the alleged breach of Clause 11.1 of the Code, the Panel noted that the clause stated that "Reprints of articles in journals must not be provided unsolicited unless the articles have been refereed". The addendum had not appeared in a journal, such as the British Medical Journal, as meant by Clause 11.1 of the Code. There could not therefore be a breach of Clause 11.1 and the Panel ruled accordingly.

The Panel noted that Clause 4.1 of the Code required that prescribing information must be provided in all promotional material except abbreviated advertisements and promotional aids. In the Panel's view the addendum constituted promotional material for alendronate, Merck Sharp & Dohme's product Fosamax. The addendum had been supplied by Merck Sharp & Dohme. It gave cost data for the product which showed an advantage over a competitor. No prescribing information was provided. A breach of Clause 4.1 was ruled.

APPEAL BY PROCTER & GAMBLE

Procter & Gamble appealed against the rejection of its complaint that the cost effectiveness comparison in the addendum had been presented in a way which was incomplete and misleading in breach of Clause 7.2 of the Code.

Procter & Gamble said that the presented cost-effectiveness analysis was erroneous, misleading and in breach of all published guidelines for the conduct of pharmacoeconomic research including the UK Guidance on Good Practice in the Conduct of Economic Evaluations

of Medicines. Under generally accepted pharmacoeconomic principles all relevant costs related to a treatment had to be taken into account in order to prevent associated design bias by including certain costs and excluding others.

In a clear breach of these principles, Merck Sharp & Dohme's analysis addressed the cost per fracture averted by simply multiplying the NNT figure by the daily acquisition cost of the medicines and by the study duration (2.9 years for FIT and 3 years for Harris). The analysis therefore failed to take into account the cost related to the treatment of the potential side effects of the treatments. Thus, though the concept of NNT itself could be defended (provided the clinical setting on which it was based was comparable to the intended use), the step from NNT to cost as undertaken by Merck Sharp & Dohme was incomplete and misleading.

It was well documented that oral treatment with alendronate gave rise in a significant proportion of patients to serious upper GI events (ie perforation, ulceration and bleeding). By making no attempt at incorporating the costs related to these and other (serious) side effects, the cost analysis was wrong. In addition the document failed to mention the use of this unorthodox methodology and as such was clearly misleading, as it gave the impression of having been properly conducted.

In addition, the NNT number derived from the FIT results was valid for the setting of a controlled clinical trial only. There was ample literature to suggest that results of clinical trials could not simply be transferred into daily clinical practice, which was particularly relevant to any type of economic analysis, and also underscored the need to include clinical practice safety costs in any calculation. Procter & Gamble referred to the supplementary information on economic evaluation of medicines that was provided in the Code.

RESPONSE FROM MERCK SHARP & DOHME

Merck Sharp & Dohme said that it appeared that Procter & Gamble accepted the principle of NNTs and the choice of studies upon which the addendum calculations were made. Procter & Gamble continued to state that it believed "the cost-effectiveness comparison in the addendum has been presented in a way that is incomplete and misleading, in breach of Clause 7.2 of the Code". However, the basis of this complaint seemed to have changed from its original letter of complaint. At that stage, Procter & Gamble seemed to accept the principle of the calculation of cost of fracture avoided by performing its own calculations. It seemed that it now objected to this principle. However, Merck Sharp & Dohme firmly believed that the data provided was clear, did not mislead and therefore did not breach the Code.

NNT was an additional tool for clinicians to use in judging efficacy, and when making the prescribing decision they should also take into account adverse effects, costs, patient characteristics, expectations and preferences. By contrast, Procter & Gamble had, in its own material, made simplistic comparisons regarding product costs with the statement "Didronel PMO is half the cost of alendronate". Three examples of such materials were enclosed. The cost per fracture avoided placed this simplistic price comparison into the context of NNT so that differences in efficacy could also be taken into account by prescribers, as well as simple daily cost, when making a prescribing decision.

The addendum was obviously not a full cost-benefit analysis. The calculation of cost per fracture saved was clearly based upon NNT study duration and cost per day. Since NNTs were duration specific it followed that the cost per fracture averted should be calculated with reference to the study duration used for the relevant NNT calculation. The costs used for the calculation were the daily acquisition costs for the two treatments. Following the listing of study durations and daily medicine costs there was an unambiguous statement "No other costs are included". Therefore, it was clear that the cost of treatment of adverse events was not included. The interpretation of adverse event data in the Harris paper regarding cyclical etidronate was complicated by the use of phosphate in two of the treatment arms.

Phosphate was not part of the UK licenced preparation of cyclical etidronate, Didronel PMO. The published data referred to diarrhoea in the first three days of cyclical treatment (corresponding to the phosphate/placebo treatment period) in 45% patients receiving phosphate and 11% of patients who did not, and hypertonia "in 4% of patients. The incidence of which was approximately threefold greater in etidronate treated patients than in non-etidronate treated patients". This adverse event data was not sufficiently detailed to be used in any meaningful economic, or number needed to harm (NNH), calculation. In FIT there were no statistically significant differences in the incidence of upper gastrointestinal adverse events and so these would not be used for a NNH calculation. It had been suggested that major harm in clinical trials could be identified by intervention-related withdrawal rates but again there was no significant difference between alendronate and placebo in FIT (7.6% vs. 9.6% respectively, p=0.123). In the addendum there was no attempt to quantify or include the costs saved by avoiding fractures eg hospitalisation costs averted. There was at present still no published peer-reviewed data for cyclical etidronate demonstrating a reduction in non-vertebral fractures, and, at the time of the Bandolier meeting, the licence for cyclical etidronate was limited to established vertebral osteoporosis. The English costs for medical treatment of hip fractures far outweighed those of vertebral fractures (in 1992/93, £237m for in-patient treatment of osteoporotic hip fractures versus £61m for outpatient and primary care treatment of all osteoporotic fractures). FIT demonstrated that alendronate reduced not only the incidence of vertebral fractures but also hip and wrist fractures and hospitalisations. Therefore, the reductions in fracture treatment and hospitalisation costs would in all likelihood favour alendronate if a full cost-benefit analysis had been done (bearing in mind the data and licence for cyclical etidronate at the time of the addendum would only allow the inclusion of vertebral fracture costs).

Merck Sharp & Dohme found the allegation from Procter & Gamble that "it is well documented that oral treatment with alendronate gives rise in a significant proportion of patients to serious upper GI events (ie perforations, ulcerations and bleeding)" outrageous. Alendronate was generally well tolerated and the occurrence of such serious upper GI events was rare. Kelly and Taggart's

experience did not include any of the serious upper GI events specifically mentioned by Procter & Gamble. Their report was uncontrolled, and upper GI symptoms were observed in 40% of the placebo group in FIT. In FIT there were no statistically significant differences in the rates of oesophageal adverse events. Colina *et al* reported a single case of oesophageal ulceration with alendronate, with the authors' subjective opinions. As such it could not support the assertion regarding "a significant proportion". Finally, the New England Journal of Medicine editorial entitled "Pill Oesophagitis - The Case of Alendronate" referenced by Procter & Gamble stated "The actual incidence of severe or serious oesophageal effects in patients taking alendronate for postmenopausal osteoporosis appears to be low". The post-marketing study discussed in the editorial clearly showed the low incidence of oesophageal adverse events in clinical use (51 serious or severe oesophageal effects in an estimated 475,000 patients treated), and when such adverse events did occur the majority seemed to have been related to inadequate adherence to the recommended dosing instructions. In any event, if a full cost-benefit analysis were to be performed any costs incurred with these rare serious upper GI adverse events were likely to be more than offset by the proven efficacy of alendronate in reducing hip fractures.

Merck Sharp & Dohme referred to Procter & Gamble's reservations about the validity of controlled clinical trials in health economics assessments and comments that "There is ample literature to suggest that the results of clinical trials cannot simply be transferred into daily clinical practice, ...". The randomised controlled clinical trial was widely viewed as the gold standard for the scientific assessment of medical interventions. In fact, references supplied by Procter & Gamble in support of its appeal contradicted its assertion. The Australian guidelines stated a strong preference for economic evaluations based on randomised controlled trials. These guidelines also specifically mentioned that they would treat controlled cohort studies (such as van Staa) with some "sceptism" (*sic*) since "It has been repeatedly shown that such studies are subject to a range of biases that frequently lead to over-estimation of the true benefit of the treatment given to the intervention group". These biases included selection, follow-up and information biases as well as confounding, and it was recommended that cohort studies were interpreted with considerable care. The likelihood of these biases was eliminated, or at least considerably reduced, in a randomised, double-blind design. Information bias was worthy of particular comment with regard to alendronate, as knowledge of the rare severe oesophageal adverse events might bias the investigation and assignation of drug causality to any upper gastrointestinal symptoms in a cohort study. It could therefore be argued (as the Australian guidelines did) that randomised controlled studies were the most appropriate for health economic analyses since they reduced bias to a minimum.

The issue of which trials were included in the analysis had already been discussed extensively and these arguments were accepted by the Panel in its original judgement. Merck Sharp & Dohme stood by the arguments presented previously in its letters. These together with the arguments stated above confirmed that whilst the NNT analysis was a perfectly valid way of presenting clinically useful information it should not be confused with a full cost-effectiveness analysis. To conclude, Merck Sharp & Dohme remained firm in its belief that the data presented in the Bandolier addendum was fully in accordance with Clause 7.2 of the Code and its supplementary information.

The company confirmed that the conference report and its addendum had been sent to those doctors who had attended the conference. In addition one copy of the material had been supplied to each of the medical representatives and a copy had also been placed on the Bandolier Website.

The company confirmed that while there were no formal presentations on the use of NNT data at the conference there would have been informal discussions on the subject and those attending would have been familiar with the concept.

FURTHER COMMENTS FROM PROCTER & GAMBLE

Introduction

Procter & Gamble submitted that, as the supplementary information to the Code made clear, the economic evaluation of medicines was a relatively new science and therefore care was required to ensure the scientific validity in making a head to head comparison between any two data sets. However scientifically valid a single comparison might be, its use in isolation should not mislead, or potentially mislead, as to the totality of the relevant evidence available on the two products. It should therefore never exaggerate the significance of the particular comparison presented or the conclusions sought to be drawn from that comparison. The assumptions and data used relating to indications, period of use, and efficacy and safety must be a) consistent with the relevant marketing authorisations, b) clinically appropriate and c) consistent with the overall evidence on the treatment. Where the data that could justifiably be compared were limited, the potential for exaggerating the significance of a single comparison selected was self evident.

Procter & Gamble suggested that on this occasion the Panel (by virtue of Merck Sharp & Dohme's focus upon the comparability of specific data sets such as to allow a specific head to head comparison) had been led to give insufficient weight to the equally critical issue of whether the efficacy comparison presented on the selected data and the subsequent extrapolation of it into a cost comparison was fair and was "based on an up to date evaluation of all the evidence and reflects that evidence clearly" and did not mislead "either directly or by implication".

Importantly, and as outlined in Procter & Gamble's letter of appeal, it was its assertion that the Merck Sharp & Dohme cost effectiveness comparison had clearly violated the numerous published and agreed health economic guidelines for the reasons outlined in detail below.

In today's cost conscious environment, consideration of this point was critical, as allowing such a precedent would open the doors for companies to use incomplete cost effectiveness analyses to influence both health professional and health authority decisions alike.

Procter & Gamble pointed out that Merck Sharp & Dohme had put forward numerous 'scientific' arguments, but in essence there were only two points of principle to consider:

1 There was the issue of whether the extrapolated cost comparison (which contained the principal claim) was fair or whether it potentially misled as to the validity of the conclusions or their significance.

2 There was the issue of whether the selection of the data sets for a single comparison was justified and was a fair reflection of the totality of the evidence relevant to comparison of the two products.

Although the above issues were linked, Procter & Gamble would deal with them separately for clarity.

1 The presentation of the NNT analysis as a sophisticated economic evaluation

The ultimate issue in this appeal was the misleading nature of the conclusions on cost effectiveness that Merck Sharp & Dohme made from the selected data set comparison presented in the addendum. It was Procter & Gamble's view that the addendum was misleading because Merck Sharp & Dohme had combined NNT analysis for both Didronel PMO and alendronate with the daily cost of each treatment. The result was a table, containing comparative costs for avoiding a fracture. This gave the clear impression that a full health economic analysis had been conducted and each figure quoted was a measure of the cost effectiveness of the respective products when used in clinical practice, when in fact it was not such a measure.

It was absolutely not acceptable for Merck Sharp & Dohme to convert the presentation of NNT based on selected efficacy data into an essentially unqualified cost effectiveness analysis (ie cost per fracture avoided) utilising only the crude measure of the acquisition cost of the product. There were clear guidelines for such analyses that included, for instance, the consideration of issues of comparative safety that could impact the cost comparison.

The requirements of a proper economic evaluation. A cost effectiveness analysis was defined as one where cost (eg monetary cost of therapy) had been related to a clinical outcome (such as one fracture averted). A cost effectiveness analysis was one of the four officially recognised types of economic evaluations that were covered by the various guidelines previously referred to. These guidelines unanimously agreed that all relevant costs should be included in an analysis. This must obviously include the direct medical costs associated with side effects:

"All those resources the use of which may be causally related to the options evaluated will be taken into account ... for example, the resources used to treat side effects or sequelae of an evaluated treatment will be counted as costs of this treatment." (Rovira J *et al*)

Direct medical costs which cover different aspects including consumption of medicines and use of medical resources (admission to hospital, outpatient appointments and medical consulting visits, laboratory tests and investigations, the cost of treatment of side effects). (Ref Guidelines and recommendations for French Pharmaco-economic studies)

In Procter & Gamble's view Merck Sharp & Dohme had failed to meet these clear standards of health economic research outlined in the published guidelines. It had made no attempt to adjust its calculations to take account of relevant costs even though it conceded that one of the factors which clinicians should take into account was adverse events. Merck Sharp & Dohme cited various reasons for not adjusting its cost effectiveness comparison to take account of each product's adverse event profile. All were misconceived.

First it was alleged that the interpretation of the adverse event data in the Harris paper was complicated by the use of phosphate in the treatment arm. Randomisation and therefore equal distribution of phosphate across the groups would not effect any difference in side effects observed between the active and control groups. Even if Procter & Gamble accepted Merck Sharp & Dohme's argument (which it did not), as it was not able to extract appropriate adverse event data and comply with the guidelines, the cost effectiveness analysis should not have been undertaken. It was not acceptable to do a sub-optimal analysis and present incomplete data as a valid exercise.

Merck Sharp & Dohme sought to pre-judge what such an analysis would show by taking issue with Procter & Gamble's reference to gastrointestinal (GI) side effects associated with use of alendronate. First, it was suggested that this adverse effect was not reflected in the clinical data selected for comparison and secondly that it was not material in clinical practice in any event.

Current scientific opinion was that clinical reality must be taken into consideration in cost effectiveness analyses where one was inviting doctors to extrapolate to every day clinical practice. The very same author that Merck Sharp & Dohme quoted as substantiation for its contrary opinion had recently published an editorial in the British Medical Journal in which he qualified his initial position. Sackett pointedly stated that each research question should be addressed using the proper study design, concluding that the randomised controlled clinical trial was not the method of choice for researching questions regarding daily clinical practice:

"Randomised controlled trials carried out in specialised units by expert care givers, designed to determine whether an intervention does more good than harm under ideal conditions, cannot tell us how experimental treatments will fare in general use, nor can they identify rare side effects. Non-experimental epidemiology can fill that gap."

Procter & Gamble referred to Merck Sharp & Dohme's statement that the randomised controlled clinical trial was widely viewed as the gold standard for scientific assessment of medical interventions. However, one could not use this principle to extrapolate conclusions to cost effectiveness in clinical practice uncritically and as an argument for ignoring known side-effects that had only become apparent after general marketing had begun.

Merck Sharp & Dohme's defence that the incidence of upper GI events in FIT was not significantly different between active and placebo treatments and, in consequence, the data could not be used in a number

needed to harm analysis was therefore not to the point. The FIT data might not have shown a statistically significant difference in the incidence of upper GI events, but this picture did not reflect clinical reality.

The GI adverse effects reported with alendronate in clinical practice were viewed by the licensing authority as sufficiently significant to add a special warning in the alendronate summary of product characteristics, despite the absence of such reports in the FIT trial. This experience in the UK was further supported by the unique collection of real life data from a major US public health provider. This extensive analysis in over 800 patients highlighted a 30% incidence rate of GI side effects in patients treated with alendronate in every day practice. The focus on GI events did not, of course, mean that other side effects could be ignored but the omission of these alone was sufficient to invalidate the exercise undertaken by Merck Sharp & Dohme.

Finally, in relation to the propriety of conducting a proper economic evaluation analysis, Merck Sharp & Dohme stated that the costs would in all likelihood favour alendronate. This was gratuitous conjecture that was not substantiated by any hard facts. It importantly highlighted an acceptance by Merck Sharp & Dohme that such matters could be relevant, which was also reflected in its attempted disclaimer.

The disclaimer by Merck Sharp & Dohme. The disclaimer "No other costings included" (which appeared as one of the brief explanatory footnotes to the table) could not be used to rectify the effect of basically misleading conclusions. Contrary to Merck Sharp & Dohme's assertion, the use of this disclaimer (which was framed in very general terms) did not make it clear that the cost of treatment of adverse events was not included. In any event, Merck Sharp & Dohme's presentation simply could not be made fair by any such disclaimer. If an exercise that purported to be a proper economic evaluation analysis was fundamentally flawed by the exclusion of critical parameters, no disclaimer could render the presentation and the claims sought to be made acceptable.

In a final attempt to justify its use of the cost effectiveness analysis, Merck Sharp & Dohme had disparaged the use of cost comparisons between Didronel PMO and alendronate, providing examples of Procter & Gamble's promotional material in substantiation. The cost comparisons made in the items cited by Merck Sharp & Dohme were straightforward product acquisition cost comparisons. Since the monetary number was in no way linked to a clinical outcome, this was not a cost effectiveness analysis. There was no pretence that the cost comparisons made were anything other, nor could they be interpreted as anything other. As such, they were therefore not relevant to this case.

In conclusion, Procter & Gamble's concern was that in today's rightly cost-conscious environment, cost of treatment (in its broadest sense) was a key factor in the prescribing decision and the Appeal Board must ensure that the provisions of the Code were applied in a way that ensured that the comparisons that companies selected did not paint an unfair or potentially misleading picture. In this present case, the simple truth was that a health professional presented with the addendum table would naturally focus on the misleading comparison in the last column. It invited him to conclude that although Didronel PMO cost 44.7 pence per day and alendronate 91.8 pence per day, the cost effectiveness of treating patients with alendronate was in fact better. In Procter & Gamble's view, Merck Sharp & Dohme's presentation and the available clinical data did not begin to justify that conclusion and was highly misleading.

2 The selection of data sets for the NNT comparison

Procter & Gamble's view was that the Appeal Board must be satisfied that proper biostatistical principles had been applied in determining that the sets of data compared were derived from studies that were methodologically sufficiently comparable to justify such a head to head comparison. These matters were not straightforward and were prone to subjective decisions being made as to the materiality of some of the types of differences that might have to be addressed. However, where one company selected the data for its own product which it wished to use and then examined what data for another product might "fit" sufficiently for a head to head comparison, there was great potential for using "comparability" as a reason for disregarding all of the other scientific data available. The need to ensure that head to head comparisons were only made where "like is compared with like" could not be used as subterfuge for avoiding the presentation of a full picture. However, this was precisely what Merck Sharp & Dohme had done and as a result its single comparison was in breach of the requirement of Clause 7.2 that any comparative claim must reflect an up-to-date analysis of all the available evidence. Merck Sharp & Dohme defended its exclusion of other efficacy data relating to Didronel PMO or time periods of comparison, on the grounds that such other data was difficult or impossible to place in a head to head comparison with its self-selected data set and period of treatment relating to alendronate.

An accepted method to reflect all available evidence, frequently used for products marketed for some time, was one that considered all relevant published data. Applying this scientific method to the data available on Didronel PMO would significantly alter any conclusions that could be drawn from the original comparison made by Merck Sharp & Dohme. Using self selected parameters, Merck Sharp & Dohme had excluded additional available efficacy data such as Storm, Watts and the cohort study by van Staa. These studies showed a more favourable outcome for Didronel PMO, confirming the overall effectiveness evidence.

In addition, the Sackett editorial emphasised the importance of non-experimental epidemiology studies. At the time of the Bandolier addendum production, such data were available for Didronel PMO. Merck Sharp & Dohme chose to ignore the largest osteoporosis study of bisphosphonate use in clinical practice (16,000 patients). The availability of these data in abstract form should have indicated to Merck Sharp & Dohme the problem of using a selected data set only.

Merck Sharp & Dohme stated that Procter & Gamble appeared to accept the choice of studies upon which the calculations were made. Notwithstanding Procter & Gamble's belief that Merck Sharp & Dohme's use of an

NNT analysis to develop a crude cost effectiveness comparison was misleading for the reasons set out above, in any event it did not agree with Merck Sharp & Dohme's choice of study. Procter & Gamble had already explained its position in this regard. Suffice to say that Merck Sharp & Dohme had to include the 3 year data from Harris which did not even meet the selection criteria it purported to have applied. This pointed very clearly to the fact that Merck Sharp & Dohme should have concluded that a head to head comparison of the type it wanted to present was not possible, but it proceeded regardless, despite the fact that the results would inevitably be so selective as to be misleading.

Merck Sharp & Dohme suggested that because of the degree to which particular issues had been argued in particular submissions, Procter & Gamble had changed its position. This was not so.

As its original correspondence with Merck Sharp & Dohme made clear, Procter & Gamble's objection had always been that the comparison Merck Sharp & Dohme chose to make was misleading both because of the data sets chosen to compare and the reasonableness of using that comparison to present or imply an overall conclusion on cost effectiveness. Where such a conclusion was to be extrapolated to day-to-day clinical practice, it must take account of direct medical costs such as those arising from treatment of product related adverse events as well as non-medical and indirect costs, as well as efficacy.

Merck Sharp & Dohme stated that Procter & Gamble appeared to accept the principle of NNTs. It did not dispute that the NNT could have value as a parameter in assessing efficacy. It accepted that the data used to calculate the NNT must be appropriate in the sense that the specific data could reasonably be compared "head to head". However, this was not a justification for an all embracing conclusion that ignored the totality of the relevant data available. Selectivity in what was presented could not be justified by reference to self serving arguments about scientific comparability of data particularly when the selected data were then extrapolated to clinical value by the use of a general cost comparison that ignored parameters such as adverse event profile.

Conclusion

Procter & Gamble stated that Merck Sharp & Dohme had clearly made a misleading cost comparison which was in breach of Clause 7.2. Procter & Gamble was not taking issue with a minor claim but a critical comparison of cost effectiveness. The link made by Merck Sharp & Dohme between the cost (monetary value) and clinical outcome (one fracture averted), suggested that a full health economic analysis had been undertaken. In this context, the analysis violated the agreed standard guidelines for health economics, as it did not include all costs (direct, indirect and other).

Supplementary to the analysis itself, the selection of data used in the comparison excluded all but a single extension study of the competitor, referable to one end point (vertebral fractures) for a single period of use, despite this being a therapy given for a chronic condition. The use of self selected criteria and disclaimers were not justification for the misleading conclusions made. Given the long marketing experience with Didronel PMO, an accepted method of reflecting all available evidence (commonly used in review articles), where all relevant published data were considered yielded significantly different results.

The Appeal Board would therefore need exceptionally good arguments from any company seeking to rely upon a simplistic comparison of the type made by Merck Sharp & Dohme before it judged that the conclusions were a fair reflection of all available evidence. With today's cost constraints, consideration of this point was critical, as such a precedent would allow companies to produce further incomplete cost effectiveness analyses to influence health professionals and health authorities.

Nothing Merck Sharp & Dohme had said in its response invalidated Procter & Gamble's fundamental objections. Merck Sharp & Dohme's promotional piece tacked onto an otherwise balanced conference report was a crude exercise masquerading as a sophisticated economic evaluation and, in Procter & Gamble's view, it was transparently likely to mislead.

APPEAL BOARD RULING

The Appeal Board noted that the letter of complaint to the Authority had criticised the papers chosen by Merck Sharp & Dohme on which to base its calculations. Procter and Gamble had expressed concern as to whether or not the papers chosen had represented the balance of the evidence. The letter had referred to past correspondence between the two companies and some of the additional arguments which were set out in those letters had been referred to in the appeal. The Appeal Board considered it unfortunate that the whole complaint had not been comprehensively and clearly set out in the original letter to the Authority. Letters of complaint should stand alone and not rely on past correspondence to set out the issues.

The Appeal Board noted that the calculation of NNT for a medicine was one parameter that described its effectiveness. In this case the NNT figure had been used, together with the cost of either etidronate tablets or alendronate tablets, to calculate the "cost per fracture saved". The Appeal Board noted however that the true cost per fracture saved would involve more than just medicine acquisition costs. The Appeal Board noted that footnotes beneath the table detailing cost per fracture saved gave brief details as to how the cost had been calculated, ie cost of the medicine and duration of therapy, and also stated "No other costings included". It was a well accepted principle under the Code, however, that claims could not be qualified by footnotes. The heading "cost per fracture saved" implied that more had been taken into account than just medicine acquisition costs and this was not so.

The Appeal Board considered that the choice of papers by Merck Sharp & Dohme was not unreasonable but questioned the basis of the calculations presented in the addendum. It was far from clear as to exactly how the figures given for "Cost per fracture saved" had been calculated. The Appeal Board noted that at the appeal hearing, the company was unable to confirm exactly how the figures had been calculated and had accepted that there was an error in the table. In addition the Appeal Board noted that the NNT for etidronate given in the table was marked non significant.

The Appeal Board noted that the conference report and its addendum had been distributed more widely than just to those who had attended the conference. Representatives had been provided with a copy and the material had been placed on the Bandolier Website. In the Appeal Board's view some readers would assume that a full economic evaluation had been undertaken and this was not so. There was not sufficient explanation of the data.

The Appeal Board considered that overall the addendum was misleading and ruled a breach of Clause 7.2 of the Code.

The complainant's appeal was therefore successful.

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Case completed 25 February 1998

CASE AUTH/617/9/97

LILLY v SMITHKLINE BEECHAM

Seroxat detail aid

Lilly alleged that a bar chart was visually misleading as the horizontal axis, which showed depression scores at weeks 1, 3, 4 and 6, had no gaps for weeks 2 and 5 when no observations were made. This had the effect of exaggerating the observed improvement. The Panel considered that it would have been preferable if weeks 2 and 5 had been incorporated into the horizontal axis even though there was no data but, in the Panel's view, the bar chart was acceptable. Data was presented at well labelled time points and was not shown in graphical form with a continuous improving curve from weeks 0 to 6. The Panel did not consider the bar chart misleading and ruled no breach.

Lilly alleged that the presentation of data from a study conveyed the impression that Seroxat had been shown to be superior in efficacy to fluoxetine (Lilly's product Prozac). It highlighted a difference in favour of Seroxat but failed to inform that there was also a difference in favour of fluoxetine and that most of the outcome measures showed no difference between them. The Panel considered that the page in question, by implying that Seroxat had earlier beneficial effects, did not reflect all of the evidence in a fair and balanced manner and ruled a breach. Upon appeal by SmithKline Beecham, the Appeal Board noted that the purpose of the study in question had been to compare efficacy and tolerability and not to look at differences in onset of action. The data appeared to suggest a trend of an earlier onset of action for Seroxat as compared to fluoxetine but the Appeal Board considered that the page in question overstated the totality of the data. Overall the Appeal Board considered that the page in general was misleading and upheld the ruling that the Code had been breached.

Lilly alleged that claims of Seroxat being highly effective in resistant depression and "effective where other antidepressants have failed" were based on inadequate evidence and were misleading. The Panel considered that the referenced study gave some support but it was not sufficient on its own to substantiate the claims. A further paper provided by SmithKline Beecham showed that while paroxetine (Seroxat) was associated with a significant improvement in symptoms from baseline and placebo treatment also showed some improvement, there was no data on the difference between the two. Overall, the Panel concluded that the claims did not reflect the evidence in a fair and balanced manner and ruled a breach.

It was alleged by Lilly that the selective quotation in the claim "In a large observation study: "Stimulatory adverse affects accounted for 30% of withdrawals of fluoxetine compared with 14.8% for other SRIs"" was not representative of all of the information presented in the study concerned and was misleading. The Panel noted that the claim dealt with adverse effects of fluoxetine therapy which included anxiety and agitation. It appeared in the middle of claims for Seroxat which dealt with its efficacy in relieving anxiety and agitation associated with depression. The data sheet for Prozac (fluoxetine) stated that it was indicated for the treatment of depressive illness with or without associated anxiety symptoms. The Panel considered that to simultaneously discuss, anxiety and agitation as a side effect with fluoxetine, and anxiety and agitation as natural components of depression, was misleading and a breach was ruled.

The vertical axis of a bar chart was labelled "Mean HAMD sleep scores". The bar chart was taken from a paper comparing Seroxat with amitriptyline. Lilly alleged that the heading "Reduction in mean HAMD sleep scores" was inaccurate as it implied that the larger the bar the larger the effect but this was not so. Though it was stated that the difference between the two medicines was not significant, the impression given was that the reductions in HAMD sleep scores were greater for Seroxat than for amitriptyline. Further the horizontal axis had been compressed exaggerating the slope of the improvement of sleep scores. The heading together with the horizontal compression was alleged by Lilly to create a visually misleading impression of the effect of Seroxat on sleep. The Panel considered that overall the combination of the claim "Matches tricyclic efficacy in improving sleep", the heading of the bar chart "Reduction in mean HAMD sleep scores" and the labelling of the vertical axis were clear and unambiguous. The Panel did not agree that the overall impression was that the reduction in HAMD sleep scores for Seroxat was greater than that for amitriptyline. The Panel noted that no efficacy evaluations were undertaken at weeks 3 and 5 but considered that the horizontal axis was clearly labelled with an appropriate space between each measurement point. The Panel did not accept that the bar chart created a misleading impression. No breach was ruled.

Lilly submitted that in two line graphs the horizontal axis was compressed since there were no gaps to indicate the absence of data points at week 5. The horizontal compression had the effect of exaggerating the slope of the improvement in HAMD scores and Lilly alleged that this created a visually misleading

impression of the information and was in breach. The Panel considered that the omission of week 5 on the axis meant that both graphs were misleading and they were ruled in breach.

Lilly said that a claim "In an elderly population (61-85 years), 'Seroxat' showed a statistically significant improvement over fluoxetine in HAMD total score at week 3 ($p<0.05$)" implied a clinical advantage for Seroxat. Lilly alleged that a selected finding from a study had been presented without reference to other information from the study, giving the impression that Seroxat had been shown to have greater efficacy than fluoxetine. This was a misrepresentation of the study and not a fair reflection of the current evidence. The Panel noted that the study used doses of fluoxetine above those recommended for depression but doses of paroxetine within the recommended range. The authors had commented that while both were effective in the treatment of elderly depressed patients paroxetine had a possible earlier antidepressant effect and earlier beneficial effect on behavioural and cognitive function. The Panel considered that the claim did not reflect all of the evidence in a fair and balanced manner and ruled it in breach. Upon appeal by SmithKline Beecham, the Appeal Board considered that the page in question overstated the data. The Appeal Board considered that readers would assume that doses in the fluoxetine study were those currently licensed for the treatment of depression and this was not so. The Appeal Board considered that the page was misleading and upheld the Panel's ruling of a breach.

Lilly alleged that a chart comparing certain antidepressants with regard to "Effect on bodyweight" was inaccurate and misleading as it stated "weight loss" for paroxetine. The Prozac data sheet stated that "Prozac may cause weight loss which may be undesirable in underweight depressed patients. Only rarely have depressed or bulimic patients been discontinued for weight loss when treated with fluoxetine". The Panel considered that the use of the unqualified phrase "weight loss" to describe the effect of Prozac upon a patient's body weight was an inaccurate summary of the Prozac data sheet and a breach was ruled.

Eli Lilly & Company Limited made a number of allegations about a Seroxat (paroxetine) detail aid (ref 05/97 ST:HD/7/017) produced by SmithKline Beecham Pharmaceuticals UK which was used by its hospital fieldforce between May and September 1997.

1 Page headed "SEROXAT - EFFICACY IN DEPRESSION"

Page 3 of the detail aid gave the results of a study by De Wilde *et al* (1993) which compared the efficacy and tolerability of Seroxat and fluoxetine (Lilly's product Prozac) in 100 patients with depression. There was a bar chart comparing the efficacy of the two products as measured by the percentage of responders to each at various times over a six week period. Responders were defined as those patients who had a reduction of more than 50% from baseline in their Hamilton Depression Rating Scale (HAMD) total score. Four time points were given, weeks 1, 3, 4 and 6. These time points were equally spaced along the x axis.

Beneath the bar chart was the claim "Seroxat showed a statistically significant improvement over fluoxetine as measured by 50% or greater reduction in HAMD and MADRS scores, and a HAMD score of 14 or less at week three".

In bold at the bottom of the page was the claim "'Seroxat' - proven efficacy in depression".

COMPLAINT

Lilly pointed out that the bar chart in the paper by De Wilde *et al* (1993) and reproduced in the promotional piece had compression of the horizontal axis. There were no gaps at week 2 and week 5 at which time no observations were made. Lilly alleged that the horizontal compression had the effect of exaggerating the slope of improvement of depression scores, thus giving a visually misleading impression of the data in breach of Clause 7.6 of the Code.

Lilly stated that in the De Wilde study the dosages of fluoxetine were in accordance with the prescribing information published in Belgium at that time. The fluoxetine treated patients all received 20mg per day in the first week and 40mg per day in the second week. The dosage thereafter was more flexible. A maximum dose of 40mg was taken by 76% of patients and a maximum dose of 60mg was taken by 22%. Lilly pointed out that these doses of fluoxetine were above those recommended for the treatment of depression in the UK (20mg per day, ref: Prozac data sheet) and submitted that patients on doses of 40-60mg might be expected to experience more adverse events than those on a dose of 20mg per day. In contrast, the patients in the paroxetine group had a more gradual increase in dose, with doubling of dose being possible only by week 4.

Lilly pointed out that of the original 100 patients 22 were excluded from the efficacy analysis. The most common reason for this was the use of proscribed concomitant medication, usually benzodiazepines. There were more 'nervous system' adverse events in the fluoxetine treated group. Lilly submitted that the data presented did not exclude the possibility that benzodiazepines might have been required to treat adverse events in patients receiving higher doses of fluoxetine. Lilly submitted that some of these patients might not have required benzodiazepines had they been treated with 20mg per day of fluoxetine and the need to exclude them might have introduced a bias into the remainder of the sample used in the efficacy analysis.

Lilly noted that of the 78 patients included in the efficacy analysis, 4 fluoxetine treated patients and 2 paroxetine treated patients withdrew due to adverse events. Lilly submitted that in a study such as this with a last observation carried forward analysis, patients withdrawing from the study would negatively effect the mean ratings of mood for the group. If the withdrawals in the fluoxetine group occurred after the increase from 20-40mg (ie, shortly after week 2) and at a later stage in the paroxetine group, this would exaggerate early differences between the groups. Lilly submitted that the data reported in this study did not permit the exclusion of this possibility.

Lilly noted that there was no statistically significant difference between the groups in change from baseline in the mean Hamilton Rating Scale for Depression (HRSD) score at any of the 4 post-baseline assessments. At week 3 there was a greater proportion of responders in the paroxetine group as defined by a reduction >50% from baseline HRSD total score ($p<0.05$) as well as by a HRSD score less than or equal to 14 ($p<0.05$).

Lilly queried what the implication would be if there was no difference between two groups in the mean score on a test but significantly more members of one group had a score below a threshold which was less than the mean? One explanation, submitted Lilly, was that this simply reflected a difference in the variance between the two groups. The group with the wider variance might have significantly more scores below a threshold which was less than the mean, but might also have more scores above a threshold which was greater than the mean. In this case, at week 3, the paroxetine group might also have had significantly more patients with scores on the HRSD above a high threshold than those in the fluoxetine group. Lilly submitted that the data reported in the study did not permit the exclusion of this possibility.

Lilly pointed out that though statistically significant differences between the groups were found at week 3 for the >50% reduction in HRSD score, HRSD score less than or equal to 14 and >50% reduction in Montgomery-Åsberg Depression Rating Scale (MDRS) score, no statistically significant differences were found at this assessment between groups in the other measures of depression (ie, change from baseline of mean HRSD, proportion with MDRS score less than or equal to 12, proportion with positive response on the Clinical Global Impression (CGI) score, or Hopkins Symptom Checklist (HSCL) score). Lilly alleged that the clinical significance of the statistically significant differences was thus doubtful.

Lilly noted that the study also reported statistically significantly greater responses in the fluoxetine treated group for scores on the HSCL at week 1. This finding, submitted Lilly, was in the opposite direction to the statistically significant findings at week 3 and no statistically significant differences between the treatment groups were found at endpoint for any of the efficacy criteria.

Lilly pointed out that in this study there were multiple assessments of depression (HRSD, MADRS, HSCL and CGI) and multiple significance tests were performed at different times. Methodological factors as outlined above might have contributed to some of the differences. Lilly submitted that since most of the comparisons showed no difference, the finding of a statistically significant difference for some of the measures in one direction at week 1 and in the opposite direction at week 3 was of doubtful clinical relevance.

Lilly stated that in the context of the promotional item, the presentation of the information from this study was done in a manner which conveyed an impression that the study showed paroxetine to be superior in efficacy to fluoxetine. It highlighted a difference in favour of paroxetine, but failed to inform that there was also a difference in favour of fluoxetine and that most of the outcome measures showed no difference between the drugs. This was a misrepresentation of the data in the study in breach of Clause 7.2 of the Code.

RESPONSE

SmithKline Beecham submitted that the bar chart shown in the detail aid was an accurate representation of the one used in the De Wilde paper with the exception that the y axis had been expanded to 100%. The company considered that this made any difference appear less than shown in the original graph. SmithKline Beecham confirmed that weeks 2 and 5 were omitted from the chart since efficacy was not evaluated at these time points. SmithKline Beecham did not accept that there was compression of the horizontal axis or that it was in breach of Clause 7.6.

SmithKline Beecham submitted that the De Wilde study appeared in a peer-reviewed journal and it had not misrepresented the data from the study.

SmithKline Beecham stated that the study by De Wilde looked at variable dosing for both Seroxat and fluoxetine. The doses used for Seroxat were within the licensed range in the UK. While the doses for fluoxetine started at the recommended UK dose of 20mg/day, there was flexible dosing after the second week, which was common practice both in terms of similar studies and in general usage. SmithKline Beecham submitted that the effect of the increase in fluoxetine dose was more likely to improve efficacy rather than produce a lower response, and was a clinically relevant comparison.

SmithKline Beecham agreed that if it was making claims for safety based on this study, the higher doses used might be relevant. However, the study was used to support efficacy claims only. SmithKline Beecham noted that Lilly was correct in stating that a maximum dose of 60mg fluoxetine was taken by 22%. However, SmithKline Beecham submitted that its efficacy claims related to the data at week 3, at which time point no patients were receiving a 60mg dose.

SmithKline Beecham stated that of the original 100 patients in the study, 22 patients were indeed excluded from the efficacy analysis, the most common reason being the use of prescribed concomitant medication, usually benzodiazepines. SmithKline Beecham had no reason to believe that these patients were receiving benzodiazepines to treat adverse events that resulted from higher doses of fluoxetine.

SmithKline Beecham stated that Lilly's suggestion that a higher number of patients in the fluoxetine group may have withdrawn from treatment due to adverse events at an early stage thereby having a negative effect on efficacy evaluations, was pure speculation. SmithKline Beecham pointed out that the De Wilde study stated that generally symptoms were more likely to occur early in treatment or when the dose was increased to the upper end of the dose range. At week 3 (when efficacy evaluation was made) the dosage of fluoxetine was 20-40mg. In both the Seroxat and fluoxetine groups, doses were only increased, where necessary, to the higher doses (40mg and 60mg, respectively) during weeks 4-6.

SmithKline Beecham confirmed that there was no statistically significant difference between groups in change from baseline in the mean HRSD score, although a significant difference was seen at week 3 in the number of responders as defined by a reduction >50% from baseline in HRSD total score ($p<0.05$), and it was this latter claim which was used in the Seroxat detail aid. The response in the Seroxat group at week 3 was also confirmed by statistically significant differences in responders as defined by a reduction >50% in MADRS total score ($p=0.05$) and a HRSD score ≤ 14 ($p<0.05$). SmithKline Beecham submitted that this was a clinically relevant finding and that it had not misrepresented this data.

SmithKline Beecham accepted that statistically significantly greater responses were seen in the fluoxetine group for scores on the HSCL at week 1, and that there were multiple assessments of depression in this study. However, the conclusion of the peer-reviewed paper was that the findings suggested that the onset of action may be earlier with paroxetine, and these findings had also been borne out by further comparative studies.

SmithKline Beecham stated that the efficacy of Seroxat and fluoxetine for depression in geriatric patients was studied by Geretsegger *et al.* A total of 106 patients received either Seroxat 20-40mg or fluoxetine 20-60mg. Efficacy was assessed at the end of weeks 1, 3 and 6 using the HAMD and MADRS rating scales. A statistically significant difference at week 3 was seen in favour of Seroxat (p=0.03) in the mean reduction in HAMD total score, although there was no significant difference in mean total MADRS scores between the two treatments at any time point. At the end of the study, a significantly higher proportion of Seroxat than fluoxetine patients had achieved a reduction of 50% or more in HAMD (p=0.03) and MADRS (p=0.04) total scores. SmithKline Beecham stated that both treatments also showed an improvement in all measures of cognitive and behavioural function, but Seroxat was significantly superior to fluoxetine at week 3. The authors of the study commented that these results indicated a possible earlier effect for Seroxat.

SmithKline Beecham submitted that two further studies , Ontiveros (1997) and Shrivastava R K *et al* (1993) had shown trends in favour of Seroxat, although statistical significance was not achieved.

Ontiveros (1997) compared Seroxat 20mg (60 patients) and fluoxetine 20mg (61 patients) and showed a trend in favour of Seroxat in reduction from baseline of HAMD scores at weeks 2 and 4, although this did not reach statistical significance.

Shrivastava R K *et al* (1993) compared Seroxat 10-50mg and fluoxetine 20-80mg in 47 patients with major depression and also noted trends in favour of Seroxat in earlier onset of action and more rapid reduction on the HAMD anxiety score at weeks 1, 2 and 3.

Two further comparative studies, Tignol (1993) and Gagiano (1993) did not show any differences between Seroxat and fluoxetine.

SmithKline Beecham submitted that it had made no claims for overall greater efficacy compared with fluoxetine, but the page in question in the detail aid was used to demonstrate that Seroxat had proven efficacy in depression, with a faster onset of action than fluoxetine.

SmithKline Beecham considered this to be a clinically relevant comparison and did not agree that the data as used was misleading or contrary to the published data.

PANEL RULING

The Panel noted that in the study by De Wilde *et al* efficacy of the two products, paroxetine and fluoxetine, was evaluated at weeks 1, 3, 4 and 6. There were no efficacy evaluations at weeks 2 and 5.

The Panel noted that the horizontal axis of the bar chart was clearly labelled with the time points weeks 1, 3, 4 and 6 but there were no spaces for weeks 2 and 5. The Panel considered that it would have been preferable if the horizontal axis had incorporated weeks 2 and 5 even though there were no data to present.

In the Panel's view, the bar chart was acceptable. Data was presented at discreet, well labelled time points. The data was not shown in graphical form with a continuous, improving curve from time 0 to week 6. Hence there was no attempt to extrapolate the data to give the impression that any results had been available at weeks 2 or 5. The Panel did not consider that the bar chart was misleading and ruled no breach of Clause 7.6 of the Code.

The Panel noted that at week 3 the percentage of patients responding to fluoxetine given in the bar chart in the detail aid was approximately 26% whereas the figure in the De Wilde paper was 16%. The Panel requested that this error be brought to the attention of both companies.

The Panel noted Lilly's point that the dose of fluoxetine used in the De Wilde study was in accordance with the prescribing information published in Belgium at the time of the study. Patients in the study received 20mg daily in the first week, 40mg in the second week and then the dose was adjusted up or down at the discretion of the investigators so that by week 4 patients could receive 20-60mg as necessary. The Panel noted that 76% of patients received a maximum daily dose of 40mg and 22% 60mg. The Panel noted SmithKline Beecham's submission that the starting dose of fluoxetine used in the study was that recommended in the UK, ie 20mg/day. The recommended dose in the Prozac data sheet for depression was 20mg/day and did not provide for an increase in dose. The recommended dose for obsessive-compulsive disorder was 20-60mg/day and the recommended dose for bulimia nervosa was 60mg/day.

The Panel noted that the text below the chart favourably compared the efficacy of Seroxat with fluoxetine at week 3 when some patients would have been taking double the recommended dose of fluoxetine. The Panel noted that the study by De Wilde was conducted between February 1989 and July 1990 and the paper was accepted for publication in October 1992 and published in 1993. The discussion section ended by stating that although the dosage schedule for both fluoxetine and paroxetine had been in line with recommendations prevailing at the start of the study, more recent data tended to confirm that 20mg/day for both compounds was the optimal dose in most patients.

The Panel noted that the bar chart gave no information as to the doses of Seroxat and fluoxetine used in the De Wilde study. In the Panel's view most readers would assume that the study had used doses of Prozac currently licensed for the treatment of depression which was not so. The Panel considered that in terms of dosage the De Wilde paper provided a misleading comparison of Seroxat and fluoxetine.

The Panel considered that there was no evidence to support the submission that the need to exclude fluoxetine treated patients receiving benzodiazepines introduced a bias into the study. The Panel noted, however, that fluoxetine was associated with a number of side effects of the nervous system including nervousness, insomnia and anxiety. These effects might be more prevalent in patients taking higher than recommended doses of fluoxetine.

The Panel considered that the submission that withdrawals from the paroxetine treated group at a later stage than the fluoxetine treated group exaggerated early differences between the two groups was speculative and unsubstantiated.

The Panel noted that the De Wilde study (1993) concluded that "Paroxetine and fluoxetine showed similar efficacy, with a greater effect on associated symptoms and possibly an earlier onset of action for paroxetine. This early result should be confirmed in further studies". The De Wilde study showed a statistically significant difference at week 3 in favour of paroxetine in terms of response rate as measured by a 50% or greater reduction in HRSD score and MADRS score and a HRSD score of 14 or less. When considering the number of patients whose total MADRS score was reduced to 12 or less at each assessment the difference was marked in favour of paroxetine at week 3 but was not significant at any of the other assessments. The Panel noted that the De Wilde study showed an earlier response at week 1 in the fluoxetine treatment group with regard to mean changes from baseline in total score and dimensional scores on the self rated HSCL. This was significantly greater for mean change in total score from baseline ($p<0.01$) and in the dimensional scores for somatization ($p<0.05$), interpersonal sensitivity ($p=0.01$) and anxiety ($p<0.001$).

The Panel also noted SmithKline Beecham's submission that the study by Geretsegger *et al* concluded that paroxetine when compared with fluoxetine had a possible earlier antidepressive effect and earlier beneficial effects on behavioural and cognitive function.

The Panel also noted SmithKline Beecham's submission that while two further studies, namely, Ontiveros (1997) and Shrivastava *et al* (1993), showed trends in favour of paroxetine, two further comparative studies, Tignol (1993) and Gagiano (1993), showed no difference between paroxetine and fluoxetine.

The Panel considered that the page in question by implying that Seroxat had earlier beneficial effects did not reflect all of the evidence in a fair and balanced manner and ruled a breach of Clause 7.2 of the Code.

APPEAL BY SMITHKLINE BEECHAM

SmithKline Beecham did not accept the Panel's comment that in terms of dosage the De Wilde paper provided a misleading comparison of Seroxat and fluoxetine.

The De Wilde study was designed before fluoxetine was available in the UK, thus the dosages used were based on prescribing information published in Belgium at that time. A variable dosing regimen was used for both Seroxat and fluoxetine, which was common practice in similar studies. The study used doses of Seroxat within the licensed range in the UK (20-40mg) and started at the recommended UK dose of 20mg/day for fluoxetine. Doses of the latter drug were then increased to 40mg for the second week and allowed flexible dosing of 20-60mg for the remainder of the study.

SmithKline Beecham had no reason to believe that the use of these higher doses of fluoxetine (maximum 40mg at week 3) would detrimentally affect the efficacy seen in this study. This increased dose was most likely to improve efficacy rather than produce a lower response, therefore it considered this to be a clinically relevant comparison. Since SmithKline Beecham did not make claims for drug tolerability based on this study, the higher doses used were irrelevant, unless they resulted in a higher rate of withdrawal from the study, which was not the case at the timepoint in question (week 3).

This study was used to support efficacy claims only. SmithKline Beecham's efficacy claims related to the data at week 3 only, at which timepoint the dosage of fluoxetine was 20-40mg.

This publication in a peer-reviewed journal studied a well matched population for severity of illness and other demographics, and there was therefore no other reason why flexible dosing should affect efficacy.

SmithKline Beecham did not accept the Panel's ruling that by implying that Seroxat had an earlier beneficial effect, the company had not reflected all the evidence in a fair and balanced manner.

The claim used in the Seroxat detail aid was "'Seroxat' showed a statistically significant improvement over fluoxetine as measured by 50% or greater reduction in HAMD and MADRS scores, and a HAMD score of 14 or less at week three" which was intended to show that there was a difference between Seroxat and fluoxetine in the early stages of treatment, ie week 3. SmithKline Beecham submitted that the claim that Seroxat had a faster onset of action was represented in a fair and balanced manner and was supported by the randomised controlled studies as discussed below.

SmithKline Beecham was grateful to the Panel for pointing out the mistake in the bar chart, whereby the percentage of patients responding to fluoxetine at week 3 should have been 16%, not 26% as shown.

A number of statistically significant findings in favour of Seroxat were found at week 3:

- Greater reduction in HRSD anxiety factor score from baseline ($p=0.01$)
- Greater number of responders defined as reduction >50% from baseline in HRSD total score ($p<0.05$)
- Greater number of responders defined as reduction >50% from baseline in MADRS total score ($p=0.05$)
- Greater number of responders defined as HRSD total score ≤14 ($p<0.05$)

In addition to the significant findings above, although this did not reach statistical significance the following trend in favour of Seroxat was also seen at week 3:

- Higher proportion with MADRS total score reduced to ≤12

An earlier response in patients receiving Seroxat was also indicated by the significant difference in favour of Seroxat seen at week 4 on the CGI severity of illness scale ($p<0.01$), with 53% in the Seroxat group showing a positive response compared with 23% in the fluoxetine group ($p<0.01$). As discussed by the authors of the paper, this delay compared with the separation noted between Seroxat and fluoxetine at week 3 in the other efficacy variables, might reflect the time taken for all symptoms, including the somatic signs of the disease, to improve.

SmithKline Beecham noted the Panel's comments that

there was a significant difference seen in the self-rated HSCL at week 1 in favour of fluoxetine, but this was not accompanied by any other significant changes in favour of fluoxetine in any other assessment in this study. The HSCL was a patient self-rating scale and as the authors commented, the results of the HSCL were not in accordance with the physician rating scales. The authors continued to note that other studies had previously shown an absence of correlation between the results of the physician-rated scales for depression and the HSCL. In addition, there was a centre effect; the change in HSCL score varied in magnitude between the three study centres and from week 3 onwards the Seroxat treated group had larger reductions in HSCL score from baseline than the fluoxetine treated patients.

In conclusion, this study clearly demonstrated that there was a difference in favour of Seroxat at week 3 in many variables. There were no significant findings in favour of fluoxetine at this or any other timepoint, other than the isolated HSCL finding discussed above. The conclusion of this peer-reviewed paper was that "Paroxetine and fluoxetine showed similar efficacy, with a greater effect on associated anxiety symptoms and possibly an earlier onset of action for paroxetine. This early result should be confirmed in further studies."

SmithKline Beecham submitted that the findings had been borne out by further randomised, controlled, comparative studies as discussed below.

The efficacy of Seroxat and fluoxetine for depression in geriatric patients was studied by Geretsegger *et al* (1994). A total of 106 patients received either Seroxat 20-40mg or fluoxetine 20-60mg. Efficacy was assessed at the end of weeks 1, 3 and 6 using the HAMD and MADRS rating scales.

The Geretsegger study also found significant differences in favour of Seroxat at week 3 in HAMD total score. SmithKline Beecham acknowledged that there were no significant differences in MADRS or CGI scores at this timepoint. However, analyses of cognitive and behavioural factors were highly clinically relevant in this elderly population and these were all statistically significant at week 3 in favour of Seroxat. The significant differences at week 3 were as follows:

- Greater reduction in mean HAMD total score (P=0.03)
- Greater mean reduction from baseline in SCAG total score (p=0.03)
- Greater mean reduction from baseline in SCAG cognitive dysfunction factor score (p=0.03)
- Greater mean reduction from baseline in HAMD cognitive factor score (p=0.03)
- Greater mean change from baseline in MMSE total score (p=0.02)

In summary, of the 7 clinical assessments undertaken at week 3, 5 were significant in favour of Seroxat, whilst none were significantly in favour of fluoxetine. The authors concluded that "By comparison with fluoxetine, paroxetine had a possible earlier antidepressant effect and earlier beneficial effect on behavioural and cognitive function". A further publication of the same study also noted these significant findings.

Three further studies whilst not showing significant differences, had shown trends in favour of an earlier onset of action of Seroxat, as discussed below.

The first was a recently published study by Ontiveros *et al* (1997) comparing Seroxat 20mg (60 patients) and fluoxetine 20mg (61 patients) and assessing efficacy by use of the HAMD and CGI scales at weeks 2, 4 and 6. Although these generally did not reach statistical significance, this study also reported trends in favour of Seroxat. These differences were:

- Greater reduction from baseline in mean HAMD total score at weeks 2 and 4.
- Higher proportion of responders with a reduction of ≥50% in HAMD total score from baseline at weeks 2 and 4.
- Greater mean reduction in HAMD sleep disturbance factor score at week 4 (p=0.033).

These authors also discussed other studies that suggested Seroxat might have an earlier onset of action than fluoxetine, and commented that "There was some suggestion of a similar effect in the current study, ...", but acknowledged that these generally did not achieve statistical significance.

A brief description of a further study Shrivastava *et al* (1993) comparing Seroxat 10-50mg and fluoxetine 20-80mg in 47 patients with major depression also noted trends in favour of Seroxat in earlier onset of action and more rapid reduction on the HAMD anxiety score at weeks 1, 2 and 3. However, full details were not provided.

Tignol *et al* compared 20mg Seroxat and 20mg fluoxetine for 6 weeks in 178 patients with major depression. Efficacy was assessed by the MADRS, CGI, HAM-A, HAD scales and a VAS for anxiety at weeks 1, 2, 3, 4 and 6. Although the findings were largely equivocal at the timepoints of interest, ie 2-4 weeks, trends were seen in favour of Seroxat. In particular, two bar charts of responders defined as a ≥50% reduction in MADRS total score and the anxiety portion of the patient-rated HAD score clearly showed differences in favour of Seroxat at weeks 2 and 4 (week 3 data were not shown).

A further comparative study Gagiano (1993) did not show any differences between Seroxat and fluoxetine. The study compared Seroxat and fluoxetine in 90 patients with major depression over 6 weeks. A flexible dosing schedule was used, to a maximum of 40mg Seroxat and 60mg fluoxetine. No significant differences were apparent in any efficacy measures and no data were available in the publication to assess early onset of action.

The early onset of action of Seroxat was further supported by placebo-controlled studies (Dunbar *et al* (1993) and Dunbar *et al* (1991)), which demonstrated improvements in depressive symptoms in the first two weeks of therapy. Significant improvement in HRSD, CGI and MADRS were seen by week 2 in Dunbar *et al* (1993). Significant improvement in HRSD, MADRS, CGI, Covi and PGE were seen by week 2 in Dunbar *et al* (1991).

To the best of SmithKline Beecham's knowledge, there were no placebo-controlled comparative studies showing early onset of action with fluoxetine at or close to UK recommended doses.

In summary, no claims for overall greater efficacy compared with fluoxetine were made, but the page was used to demonstrate that Seroxat had proven efficacy in depression, with a faster onset of action than fluoxetine.

Of the randomised, controlled, comparative studies described above, two provided evidence of a significant earlier onset of action with Seroxat than fluoxetine, three provided evidence of trends in favour of earlier onset of action of Seroxat, and the other found the two to be equivocal. SmithKline Beecham believed this strongly indicated that the current published evidence supported the earlier beneficial effects of Seroxat in a fair and balanced manner. It did not believe it to be in breach of Clause 7.2 of the Code.

APPEAL BOARD RULING

The Appeal Board noted that the purpose of the De Wilde study was to compare the efficacy and tolerability of paroxetine and fluoxetine and not to look at differences in onset of action. The Appeal Board noted that the De Wilde study stated that paroxetine and fluoxetine showed similar efficacy, with a greater effect on associated anxiety symptoms and possibly an earlier onset of action for paroxetine and that this early result should be confirmed in further studies.

The Appeal Board accepted that the data appeared to suggest there was a trend of an earlier onset for action for Seroxat compared to fluoxetine. The Appeal Board considered that the page overstated the totality of the data.

The Appeal Board considered that readers would assume that the fluoxetine doses used were those currently licensed for the treatment of depression in the UK and this was not so. The page of the detail aid in question did not provide information about the dosage used. The Appeal Board considered this omission to be misleading.

Overall the Appeal Board considered that the page in question was misleading. The Appeal Board therefore upheld the Panel's ruling of a breach of Clause 7.2 of the Code.

The appeal on this point therefore failed.

2 Claims "HIGHLY EFFECTIVE IN SEVERE AND RESISTANT DEPRESSION" and " 'Seroxat' - effective where other antidepressants have failed"

Page 4 of the detail aid included a bar chart comparing Seroxat and imipramine with regard to change in mean HAMD total score. Beneath the bar chart was the claim "Effective in 69% of cases previously resistant to antidepressant therapy (mainly amitriptyline)", following the claim was a bar chart referenced to a study by Gagiano *et al* 1988. The bar chart showed the percentage of patients showing a good therapeutic response to Seroxat and was followed by the claim "...effective where other antidepressants have failed".

COMPLAINT

Lilly referred to a page headed "HIGHLY EFFECTIVE IN SEVERE AND RESISTANT DEPRESSION". In support of the latter part of the statement was a bar chart derived from a paper by Gagiano *et al* (1988). Lilly stated that this paper gave a brief description of a 6 week open study of paroxetine in 28 patients who had HAMD scores of 18 or more while receiving alternative antidepressants. The only description of the sample was that they were adults (7 males and 21 females) comparable in terms of age and weight. Other than a minimum HAMD score, the fact that they were on an antidepressant other than paroxetine, and that they "had not previously responded to antidepressant therapy" no other information was given. Lilly submitted that the claim that these were "cases previously resistant to antidepressant therapy" could not be made without information about their past history and treatment. Lilly pointed out that two patients were withdrawn after 2 weeks and 8 further patients failed to complete the study - 7 of whom were reported as having a poor therapeutic response. The remaining 18 patients were described as having "a good therapeutic response", though no clear outcome criteria were stated. The only outcome measure given was that the 18 patients had a mean HAMD score of 6.4 at the end of the study. Lilly submitted that the data reported in this paper was of little value in assessing the efficacy of paroxetine in resistant depression and that claims of being highly effective in resistant depression and "effective where other antidepressants have failed" were based on inadequate data and were thus misleading in breach of Clause 7.2 of the Code.

RESPONSE

SmithKline Beecham stated that the relevant section referred to the efficacy of Seroxat in treating patients with resistant depression. Patients with resistant depression were notoriously difficult to treat and very few randomised controlled studies had been carried out in these patients. As a result most of the published data on the treatment of these patients was reported as small open studies.

The reference used to support the claims made in the detail aid, Gagiano (1988) was an open study in patients with major depression who had not previously responded to antidepressant therapy. Many of these patients (15 out of 28) had previously received a tricyclic antidepressant, amitriptyline. Eighteen of the 26 patients (69.2%) assessed showed a good therapeutic response to Seroxat.

SmithKline Beecham submitted that Tyrer *et al* (1987) supported the efficacy of Seroxat in the treatment of depression. This study investigated the effects of Seroxat (30mg daily) in 24 patients with resistant depression who had failed to respond to conventional antidepressants after at least four weeks of treatment. In this placebo-controlled study, all patients received 6 weeks of Seroxat treatment, beginning and ending with a placebo phase. All 20 patients who completed the study showed a significant improvement of symptoms after four weeks of Seroxat.

SmithKline Beecham submitted that the claims at issue were justified.

PANEL RULING

The Panel noted that the Gagiano paper referenced to support the claims "Highly effective in severe and

resistant depression" and "Seroxat - effective where other antidepressants have failed" was an open six week study using 30mg paroxetine in 28 patients who had not previously responded to antidepressant therapy. Twenty six patients were assessed of which 18 (69.2%) showed a good therapeutic response. The Panel therefore considered that the referenced study gave some support to the claim but the fact that the study was of an open design with no placebo control group meant that it was not sufficient, on its own, to substantiate the strong efficacy claims in question. A cited reference did not, however, need to provide complete substantiation. It would be possible for additional material to be provided to substantiate claims. SmithKline Beecham had provided a second study, Tyrer *et al* (1987).

The Panel noted that the Tyrer study was a double-placebo crossover design in 24 patients with resistant depression who had failed to respond to conventional antidepressants after at least 4 weeks of treatment. Following an initial placebo phase of either 2 or 4 weeks almost all patients took 30mg of paroxetine daily. Paroxetine was associated with a significant improvement in symptoms from baseline. The Panel noted however that there was some improvement on placebo compared to baseline. The Panel considered that the relevant factor was the difference between paroxetine treatment and placebo treatment which would give information about the efficacy of paroxetine. There was no data on this point in the study. The Panel noted that the authors of the study stated that "Although these data are insufficient in themselves to indicate a specific place of 5-HT reuptake inhibitors in the treatment of resistant depression they point the need for further enquiry".

Overall the Panel considered that the claims in question did not reflect the evidence in a fair and balanced manner. A breach of Clause 7.2 was ruled.

3 Claim "Stimulatory adverse affects* accounted for 30% of withdrawals of fluoxetine compared with 14.8% for other SRIs"

Page 5 headed " 'SEROXAT' - RELIEVES ANXIETY ASSOCIATED WITH DEPRESSION" referred to the prevalence of anxiety and agitation in depression, the efficacy of paroxetine in relieving depression-associated anxiety and a graph showing a comparison between paroxetine and amitriptyline in relieving associated anxiety. This was followed by the statement "In a large observation study: "Stimulatory adverse affects* accounted for 30% of withdrawals of fluoxetine compared with 14.8% for other SRIs"", referenced to a paper by Martin *et al* (1997). This was followed by a statement "Seroxat - an SSRI that reduces anxiety and agitation". Explanation for the asterisk was given at the foot of the page as "agitation, anxiety, panic attacks, hallucinations, insomnia and nightmares".

COMPLAINT

Lilly stated that the interposition of the negative statement about fluoxetine and stimulatory adverse events between the positive statements about the efficacy of paroxetine in relieving depression-associated anxiety implied that paroxetine had superior efficacy in this regard.

Lilly stated that relief of anxiety associated with depression was not the same as agitation/anxiety as an adverse event. Fluoxetine had been shown to be effective in relieving anxiety associated with depression (Schatzberg, (1995)). This was reflected in its data sheet indication for the "treatment of symptoms of depressive illness with or without associated anxiety symptoms" (ref Prozac data sheet). Indeed, Lilly pointed out that in a SmithKline Beecham study (Tignol (1993)), fluoxetine and paroxetine were shown to have equal efficacy in the relief of symptoms of anxiety associated with depression. This study reported anxiety-related adverse events in 13.5% of the patients treated with paroxetine and 11.5% of the patients treated with fluoxetine. Lilly submitted that the out-of-context quotation from the study by Martin *et al* (1997) conveyed a misleading impression of the magnitude of the problem.

Lilly submitted that the figures quoted referred to stimulatory adverse events as a proportion of withdrawals but gave no indication of the frequency as a proportion of all prescriptions. Expressed in this manner, Lilly submitted that the data for fluoxetine and paroxetine showed that 3% of patients prescribed fluoxetine were discontinued from the medication due to stimulatory adverse events compared to 1.8% of patients prescribed paroxetine. Overall, adverse effects were the reason for discontinuation of medication for 11.1% of patients prescribed paroxetine compared to 10.1% of patients prescribed fluoxetine. The proportion of discontinuations due to stimulation and headache was greater in patients on fluoxetine, but the proportion of discontinuations due to gastrointestinal adverse events, lethargy and other CNS events was greater in patients on paroxetine.

Lilly alleged that the selective quotation in the claim "In a large observation study: "Stimulatory adverse affects* accounted for 30% of withdrawals of fluoxetine compared with 14.8% for other SRIs"" was not representative of all the information presented in the study and was misleading. A breach of Clause 7.2 was alleged.

RESPONSE

SmithKline Beecham stated that the page in question referred to the likelihood of anxiety and agitation being present in depressed subjects, and the efficacy of Seroxat (compared with amitriptyline) in reducing such anxiety.

Since the launch of Seroxat, it had been indicated for the treatment of symptoms of depressive illness, including depression accompanied by anxiety. Fluoxetine had more recently gained an additional indication for anxiety.

Paradoxically, with some antidepressants, a transient increase in anxiety symptoms including agitation, had been observed when treatment was initiated (Montgomery 1989). This had been reported to occur with fluoxetine (Gorman *et al* 1987).

SmithKline Beecham stated that a Drug and Therapeutics Bulletin (1993) that compared the available SSRIs for depression reported that anxiety and agitation occurred more commonly with fluoxetine (15%) than with other SSRIs (1-8%). A review of side effects seen in 1378 patients who took part in fluoxetine clinical studies found that "nervousness" was the second most commonly reported side effect, experienced by approximately 20% of patients

treated with fluoxetine. This rate was significantly higher than in patients who received doxepin or placebo (Wernicke (1985)).

A safety update in 4336 patients in comparative clinical trials (Cooper (1988)) also reported that fluoxetine-treated patients had a higher incidence of nervousness than patients treated with comparison drug or placebo.

SmithKline Beecham stated that Beasley *et al* (1992) analysed reports of "activation" associated with fluoxetine, where the adverse events nervousness, anxiety, agitation and insomnia were considered indicative of activation. Activation was considered a statistically significant treatment-emergent phenomenon, and was reported in up to 32% of patients on fluoxetine.

In contrast, SmithKline Beecham submitted that in a study by Dunbar and Fuell (1992) Seroxat had been shown to prevent emergence of anxiety and agitation in depressed patients. The study investigated the effect of Seroxat on anxiety symptoms, including the emergence of new anxiety and agitation, using a total database of 4668 patients. In patients with little or no anxiety at the start of treatment, Seroxat did not cause emergent psychic or somatic anxiety any more often than either placebo or active control (mainly tricyclic antidepressants, which were generally thought to be sedating and therefore were associated with anti-anxiety properties). Seroxat also significantly prevented the appearance of emergent agitation.

SmithKline Beecham submitted that the claim at issue referred to a peer reviewed paper by Martin *et al* (1997). This was a large observational study that included assessments of 3934 courses of antidepressants that were discontinued, including an analysis of the reason for stopping or changing therapy. The quote "Stimulatory adverse effects accounted for 30% of withdrawals of fluoxetine compared with 14.8% for other serotonin reuptake inhibitors" was taken directly from the paper, where stimulatory adverse effects were defined as agitation, anxiety, panic attacks, hallucinations, insomnia and nightmares.

SmithKline Beecham submitted that the data presented by Lilly was not taken directly from the paper, but had been calculated from the data provided in the paper and Lilly had made its own interpretation of these figures which SmithKline Beecham considered was inappropriate.

SmithKline Beecham did not believe the quote used was misrepresentative of the data presented in the study, but that it was truly reflective of the nature of the adverse event profiles seen with these medicines.

SmithKline Beecham did not refute Lilly's claim that fluoxetine was efficacious in relieving anxiety in depressed patients. There was no implied link between relief of anxiety associated with depression and anxiety/agitation as an adverse event. SmithKline Beecham submitted that the layout of the page did not question the efficacy of fluoxetine in anxiety and the use of the statement was clinically relevant.

PANEL RULING

The Panel noted that the claim "..."Stimulatory adverse affects* accounted for 30% of withdrawals of fluoxetine compared with 14.8% with other SRIs"" dealt with adverse effects of fluoxetine therapy which included anxiety and agitation. The Panel noted that the claim was in the middle of claims for Seroxat which dealt with its efficacy in relieving anxiety and agitation associated with depression. It further noted that the Prozac data sheet stated that Prozac was indicated for the treatment of depressive illness with or without associated anxiety symptoms. The Panel considered that to mix up the two issues, anxiety and agitation as a side effect with fluoxetine and anxiety and agitation as natural components of depression, was misleading. A breach of Clause 7.2 was ruled.

4 Bar chart headed "REDUCTION IN MEAN HAMD SLEEP SCORES"

Page 7 headed " 'SEROXAT' - AN SSRI THAT RESTORES NORMAL SLEEP", included a bar chart headed "REDUCTION IN MEAN HAMD SLEEP SCORES". The vertical axis of the bar chart was labelled "Mean HAMD sleep score". The bar chart was derived from a paper by Hutchinson *et al* (1991) and compared Seroxat with amitriptyline.

COMPLAINT

Lilly submitted that the heading of the bar chart implied that the larger the bar, the greater the effect, but it was only on reading the vertical axis that it was clear that this was not the case. Though it was stated that the difference between Seroxat and amitriptyline was not significant, the visual impression created by reading the heading and observing the bars was that the reductions in HAMD sleep scores for paroxetine were greater than those for amitriptyline. Furthermore, Lilly noted that there was compression of the horizontal axis, there was no gaps at week 3 and week 5 which, alleged Lilly, exaggerated the slope of the improvement of HAMD sleep scores.

Lilly submitted that the heading "REDUCTION IN MEAN HAMD SLEEP SCORES" was inaccurate which together with the horizontal compression of the chart created a visually misleading impression of the effect of paroxetine on sleep. Lilly alleged a breach of Clause 7.6 of the Code.

RESPONSE

SmithKline Beecham submitted that around 90% of depressed patients experienced disturbances in sleep patterns, and this was in fact one of the criteria used for diagnosing depression. An antidepressant that improved sleep would help a depressed patient to feel better and be able to function better the following day. SmithKline Beecham stated that this page of the detail aid was designed to show that 'Seroxat' had beneficial effects on sleep in these patients. It was widely accepted that tricyclic antidepressants, such as amitriptyline, helped patients to sleep and therefore a comparison of Seroxat and amitriptyline was clinically relevant.

The bar chart used to demonstrate this beneficial effect of Seroxat on sleep was taken from a comparative study with amitriptyline by Hutchinson *et al*. Patients were assessed at baseline, weeks 1, 2, 4 and 6 using a number of efficacy measures, including the HAMD rating scale. The HAMD rating scale consisted of 21 items, including a

number relating to sleep disturbance.

The bar chart used showed the mean HAMD sleep scores for Seroxat an amitriptyline at the different time points and demonstrated that both Seroxat and amitriptyline reduced the mean HAMD sleep scores. SmithKline Beecham stated that it was not its intention to show that Seroxat was superior to amitriptyline in improving sleep, only that it was equivalent. SmithKline Beecham did not accept that the bar chart implied superiority for Seroxat. At the bottom of the chart it was clearly indicated that there was no significant difference in the effect seen with these two drugs, and in addition, the chart appeared beneath the claim "Matches tricyclic efficacy in improving sleep". SmithKline Beecham did not consider "Reduction in mean HAMD sleep scores" to be inaccurate in breach of the Code as the chart clearly showed a reduction in mean HAMD sleep scores.

SmithKline Beecham submitted that the bar chart used was an accurate representation of the one used in the paper. There were no bars for weeks 3 and 5 since no efficacy evaluations were done at these time points.

PANEL RULING

The Panel considered that overall the combination of the claim "Matches tricyclic efficacy in improving sleep", the heading of the bar chart "Reduction in mean HAMD sleep scores" and the labelling of the vertical axis were clear and unambiguous. The Panel did not accept that the overall impression created by reading the heading and observing the bars was that the reduction in HAMD sleep scores for Seroxat was greater than those for amitriptyline.

The Panel noted that no efficacy evaluations were undertaken at weeks 3 and 5. The Panel considered that the horizontal axis was clearly labelled with an appropriate space between each measurement point. Whilst the Panel accepted that weeks 3 and 5 were missing from the horizontal axis it did not accept that the bar chart created a misleading impression.

The Panel ruled no breach of Clause 7.6 of the Code.

5 Misleading graphs

Page 11 headed "'Seroxat' - onset of action" included two line graphs comparing Seroxat and placebo. These were labelled 'Weekly analysis of HAMD sleep scores' and 'Weekly analysis of HAMD total scores'. Five time points were given along each x axis, weeks 1, 2, 3, 4 and 6. These were equally spaced along the x axis with no space for week 5.

COMPLAINT

Lilly submitted that the two graphs had compression of the horizontal axis, since there were no gaps to indicate the absence of a data points at week 5. The horizontal compression had the effect of exaggerating the slope of the improvement of HAMD scores. Lilly alleged that this created a visually misleading impression of the information and was in breach of Clause 7.6 of the Code.

RESPONSE

SmithKline Beecham submitted that the page in question was designed to demonstrate that Seroxat therapy resulted in an improvement in sleep and in the symptoms of depression after only 1-2 weeks of treatment and this was maintained over the treatment period.

SmithKline Beecham stated that the two graphs shown in the detail aid were referenced to Dunbar *et al* (1993), a double-blind study comparing the efficacy and safety of Seroxat and placebo. Efficacy assessments were conducted at baseline and weeks 1, 2, 3, 4 and 6. Since there was no measurement at week 5, this data point was not included on the graphs.

SmithKline Beecham submitted that the first graph, on compression, showed no difference whatsoever as the graph was flat between these time points.

SmithKline Beecham noted that the second graph showed some differences between weeks 4 and 6, causing a slope which would decrease if the x axis were extended, but stated that both weeks 4 and 6 showed statistically significant differences between Seroxat and placebo, and therefore presenting the graph in this manner did not alter the clinical interpretation.

PANEL RULING

The Panel noted that the graphs in question were both line graphs where data from different evaluation points had been joined together in a continuous improving curve. The Panel considered that compression of the x axis in such a graph would have the effect of exaggerating a curve. The Panel noted that in the first graph the curve was flat between weeks 4 and 6. In the second graph the placebo curve had flattened between weeks 4 and 6 although the Seroxat curve continued to show a decline the slope of which was exaggerated by the compression of the x axis. Notwithstanding the flattened curve in the first graph the Panel considered that omission of week 5 on the x axis meant that both graphs were misleading. A breach of Clause 7.6 was ruled.

6 Claim "In an elderly population (61-85 years), Seroxat showed a statistically significant improvement over fluoxetine in HAMD total score at week 3 ($p<0.05$)"

COMPLAINT

Lilly stated that the claim, which was referenced to a study by Geretsegger *et al* (1994) and appeared on page 19 headed "'Seroxat' - in the elderly", implied a clinical advantage for paroxetine.

Lilly noted that the paper by Geretsegger *et al* (1994) described a SmithKline Beecham sponsored double-blind randomised study of 106 elderly depressed patients comparing the efficacy of paroxetine and fluoxetine. Lilly submitted that the paper did not fully describe some factors which might have had a relationship to the findings of the study.

Lilly noted that the patients received either paroxetine 20-40mg per day or fluoxetine 20-60mg per day. The proportion of patients receiving particular doses and the average dose were not stated. The fluoxetine dose was above that licensed for the treatment of depression in the UK (20mg per day). Patients receiving greater than this

dose might be expected to experience more adverse events than those on a dose of 20mg per day. Lilly submitted that as with the study by De Wilde *et al* (1993) patients dropping out due to adverse events might have elevated total depression scores for the sample in a last observation carried forward design and the presentation of the data in the study did not exclude this possibility.

Lilly stated that the study referred to "...a significant between-group difference in HAMD total score in favour of paroxetine at the end of Week 3 (p=0.03, Fig 1)". The legend to figure 1 which showed the mean HAMD total score over time, read "p=0.03 for the mean change from baseline by comparison with fluoxetine". Lilly submitted that these two statements implied different forms of analysis. It was not clear which method was used. With the HAMD there could be large variability in values at baseline and post-baseline. The method for incorporating baseline could therefore have a large impact on significance. The method for incorporating the baseline was not made explicit in the paper.

The paper did not justify the sample size and made it unclear as to what power was specified in order to determine a clinically relevant difference. The magnitude of the difference at week three was not stated in the paper. Clinical relevance depended on the magnitude of the difference as well as statistical significance.

Lilly submitted that in a study such as this with multiple assessments of depression (HAMD, MADRS and CGI) in which multiple significance tests were performed at different times, attributing clinical relevance to a single significant difference might be misleading. The three assessments were made serially on three occasions post baseline. The study reported no difference between the groups on other measures of depression at any time point. The significant difference with p=0.03 in one test out of nine, with the others showing no difference, suggested that this was not a clinically relevant finding.

Lilly pointed out that the paper also did not make clear what the primary end-point of the study was (ie, what test criterion at what time point). The fact that the study was conducted over 6 weeks suggested that this was the primary end point for comparison. Since there was no difference at 6 weeks the relevance of a difference at 3 weeks was not clear.

Lilly submitted that the promotional item presented a selected finding without reference to the other information from the study, giving the impression that the study found paroxetine to have greater efficacy than fluoxetine. This was a misrepresentation of the study and was not a fair reflection of current evidence. Lilly alleged that the claim was in breach of Clause 7.2 of the Code.

RESPONSE

SmithKline Beecham submitted that the page in question demonstrated the suitability of Seroxat for the treatment of depression in the elderly. The claim at issue referred to a comparative study of Seroxat and fluoxetine by Geretsegger *et al* (1994) which had been peer-reviewed. The company submitted that it had not misrepresented the data.

SmithKline Beecham stated that the Geretsegger study also used a flexible dosing regimen for both Seroxat and fluoxetine, starting at the recommended UK dose of 20mg/day and allowing higher doses (maximum of 40mg Seroxat and 60mg fluoxetine), in line with other studies and clinical practice. SmithKline Beecham submitted this increase in fluoxetine dose was most likely to have resulted in improved efficacy rather than the opposite and the data presented in the detail aid was an accurate representation of the contents and overall findings of the study which had been supported by other studies.

SmithKline Beecham stated that the mean HAMD total scores were shown in the first graph and a clear difference could be seen at week 3, this difference being statistically significant (p=0.03).

SmithKline Beecham referred to Lilly's allegation that the study reported no differences between groups on other measures of depression at any time point and thus the statistically significant difference in mean HAMD score at week 3 was not clinically relevant. SmithKline Beecham submitted that this was incorrect as other significant differences were reported in the paper. At the end of treatment, the study found there was a significantly higher proportion of responders to Seroxat than to fluoxetine, as shown by the reduction of 50% or more in HAMD (p=0.03) and MADRS (p=0.04) total scores.

SmithKline Beecham pointed out that in addition, further significant findings were reported at week 3 in cognitive and behavioural changes. The conclusion of this study was that Seroxat had a possible earlier antidepressant effect. The findings were also confirmed by similar results in the De Wilde study and other comparative trials, eg Ontiveros (1997) and Shrivastava *et al* (1993), as discussed under point 1. Two further comparative studies found no differences between Seroxat and fluoxetine, namely Tignol (1993) and Gagiano (1993).

SmithKline Beecham submitted that there was a significant difference at week 6 in the proportion of responders to Seroxat compared with fluoxetine, as shown as reduction of 50% or more in HAMD and MADRS total scores, and in summary at both weeks 3 and 6 many parameters measured showed Seroxat to be superior to fluoxetine.

PANEL RULING

The Panel noted that the Geretsegger study had used doses of fluoxetine (20-60mg/day) above the recommended daily dose for depression of 20mg/day. Doses of paroxetine (20-40mg/day), however, were within the recommended dose range of up to 50mg/day.

The Panel noted that while there was a significant difference between fluoxetine and paroxetine in terms of HAMD total scores and other parameters at week 3, there was no difference in the mean total MADRS scores between the two products at any time point. By week 6 many of the parameters measured showed no difference between the two medicines although there were a high proportion of responders in the paroxetine treated group as defined by a reduction of 50% or more in HAMD or MADRS total scores. The Panel noted that the authors of the study concluded that while both paroxetine and fluoxetine were effective in the treatment of elderly depressed patients, by comparison paroxetine had a possible earlier antidepressant effect and earlier beneficial

effect on behavioural and cognitive function.

In view of the findings of the Geretsegger study, the Panel considered that the claim "In an elderly population (61-85 years), Seroxat showed a statistically significant improvement over fluoxetine in HAMD total score at week 3 ($p<0.05$)" did not reflect all of the evidence in a fair and balanced manner and ruled a breach of Clause 7.2 of the Code.

APPEAL BY SMITHKLINE BEECHAM

SmithKline Beecham did not accept the Panel's ruling that the claim did not reflect all the evidence in a fair and balanced manner.

As discussed in point 1, there was evidence from comparative studies to support an earlier antidepressant effect with Seroxat compared with fluoxetine. One of these studies, Geretsegger *et al* (1994), compared the effect of Seroxat and fluoxetine specifically in an elderly population.

The page in question demonstrated the suitability of Seroxat for the treatment of depression in the elderly. The claim appeared at the bottom of the page, "In an elderly population (61-85 years), Seroxat showed a statistically significant improvement over fluoxetine in HAMD total score at week 3 ($p<0.05$)" and was intended to reflect the authors' conclusion that Seroxat had a possible earlier antidepressant effect (at week 3) in this patient population. SmithKline Beecham had no intention of implying that Seroxat had greater overall efficacy than fluoxetine.

The claim referred to the Geretsegger study of Seroxat and fluoxetine published in a peer-reviewed journal. A total of 106 patients received either Seroxat 20-40mg or fluoxetine 20-60mg. Efficacy was assessed at the end of weeks 1, 3 and 6 using the HAMD and MADRS rating scales.

This was the only study in the elderly which compared the two products and SmithKline Beecham believed the findings were clinically relevant and reflected the current body of evidence in this population. This study found significant differences in favour of Seroxat at week 3 in HAMD total score. SmithKline Beecham acknowledged there were no significant differences in MADRS or CGI scores. Analyses of cognitive and behavioural factors were also highly clinically relevant in this elderly population since the effect of therapy on cognitive function could prevent the patient achieving a full therapeutic response. The measures of cognitive and behavioural function all demonstrated significant differences for Seroxat over fluoxetine at week 3.

The significant differences found in this study at week 3 were as follows:

- Greater reduction in mean HAMD total score ($p=0.03$).
- Greater mean reduction from baseline in SCAG total score ($p=0.03$).
- Greater mean reduction from baseline in SCAG cognitive dysfunction factor score ($p=0.03$).
- Greater mean reduction from baseline in HAMD cognitive factor score ($p=0.03$).
- Greater mean change from baseline in MMSE total score ($p=0.02$).

As previously described, of these 7 clinical assessments, 5 were significant in favour of Seroxat, whilst none were significantly in favour of fluoxetine.

The discussion stated:

"Both paroxetine and fluoxetine produced improvements in all measures of cognitive and behavioural function; however, paroxetine showed superiority over fluoxetine by Week 3 of treatment. Subscale analysis of SCAG scores showed that the difference between the groups was increased by the end of treatment."

The possible early effect of paroxetine observed in this study confirms the findings of a previous double-blind comparison of paroxetine and fluoxetine in depressed patients (De Wilde *et al*, (1991)) and substantiates those of a multicentre comparison of paroxetine and imipramine (Dunbar *et al*, (1991))".

Furthermore, the authors concluded "By comparison with fluoxetine, paroxetine had a possible earlier antidepressant effect and earlier beneficial effect on behavioural and cognitive function". A further publication Schone *et al* (1993) of the same study also noted these significant findings.

SmithKline Beecham did not agree that the use of this finding was a misrepresentation of the study and considered it a fair and balanced reflection of the current evidence in elderly patients. It did not believe it was in breach of Clause 7.2 of the Code.

APPEAL BOARD RULING

The Appeal Board noted that the Geretsegger study compared the antidepressant efficacy of paroxetine in the treatment of elderly depressed patients with fluoxetine. The products were also assessed for their effects on cognitive and behavioural function. It was not a study looking at differences in onset of action. The Appeal Board noted that the study concluded that paroxetine had a possible earlier antidepressant effect.

The Appeal Board considered that the data appeared to suggest there was a trend of an earlier onset of action for Seroxat compared to fluoxetine. The Appeal Board considered that the page overstated the data.

The Appeal Board considered that readers would assume that the fluoxetine doses were those currently licensed for the treatment of depression and this was not so.

Overall, the Appeal Board considered that the page was misleading. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 of the Code.

The appeal on this point therefore failed.

7 Chart comparing Seroxat, fluoxetine and other antidepressants

The penultimate page of the detail aid included a chart comparing the features of certain antidepressants with regard to the feature "Effect on bodyweight". The chart stated "no change" in a column headed "Seroxat" and "weight loss" in the column headed "fluoxetine". The material was referenced to the relevant data sheets.

COMPLAINT

Lilly stated that the Prozac data sheet read "Prozac may cause weight loss which may be undesirable in underweight depressed patients. Only rarely have depressed or bulimic patients been discontinued for weight loss when treated with fluoxetine". Lilly submitted that to summarise this as "Weight loss" was inaccurate and misleading and in breach of Clause 7.2 of the Code.

RESPONSE

SmithKline Beecham stated that weight loss was a common symptom of depression, and was one of the diagnostic criteria for depression. That an antidepressant caused weight loss was clinically relevant.

The fluoxetine data sheet stated that the drug might cause weight loss which might be undesirable in underweight depressed patients. Further data supported the effect of fluoxetine on bodyweight. In a safety review of fluoxetine, Cooper *et al* (1988) commented that in clinical trials, fluoxetine-treated patients generally experienced weight loss, which was directly proportional to the patient's body weight at the initiation of therapy. Patients who were markedly obese lost an average of 7lb during the first 6 weeks of therapy, whereas those who were not overweight lost an average of 2lb. By comparison, patients on tricyclic antidepressants in comparative studies, generally gained about 1lb after 6 weeks of therapy. Weight gain was generally accepted to be associated with tricyclics.

SmithKline Beecham therefore submitted that summarising fluoxetine's effect on bodyweight as "Weight loss" was not misleading, and was not in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel considered that the use of the unqualified phrase "weight loss" to describe the effect of Prozac upon a patient's bodyweight was an inaccurate summary of the Prozac data sheet which stated that Prozac may cause weight loss. The Panel ruled a breach of Clause 7.2 of the Code.

Complaint received **26 September 1997**

Case completed **1 April 1998**

GENERAL PRACTITIONER v SANKYO PHARMA

Conduct of a representative

A general practitioner complained about the failure of a representative from Sankyo Pharma to keep an appointment.

Sankyo submitted that a different representative to the one that had made the appointment had kept the appointment but had arrived late as he had difficulty in finding the surgery.

The Panel ruled no breach of the Code as the representative had acted responsibly and courteously by telephoning ahead to ask for directions and to advise that he would be late. The Panel noted there were differences between each party's description of the events in question.

The complainant appealed the matter to the Appeal Board. The complainant stated that nobody turned up at the surgery on the day of the appointment. This was disputed by Sankyo.

The Appeal Board considered that as the matter concerned an issue of fact which could not be properly resolved without the oral evidence of the people involved, the Chairman should invite the complainant and the representative to attend the meeting. Both parties attended and provided documentary evidence.

The Appeal Board noted that there were inconsistencies as to what was actually said in the telephone conversation. Having considered the representative's schedule for the morning and his description of the surgery, the Appeal Board's view was that, on the balance of probabilities, the representative had not kept his appointment with the complainant.

The Appeal Board noted that following the telephone call from the representative, the complainant knew that the appointment had been cancelled. This had been recorded in the practice diary. The Appeal Board considered that the representative had acted appropriately in telephoning the surgery as quickly as he could once he realised the correct location of the sugery. It was unfortunate that the complainant had been kept waiting a few minutes before receiving information about the representative's telephone call but this was not a breach of the Code. The Appeal Board therefore upheld the ruling of no breach of the Code.

A general practitioner wrote to Sankyo Pharma UK Limited to complain about the conduct of one of its representatives. The letter was copied to the Authority and the matter was dealt with as a complaint under the Code.

COMPLAINT

The complainant stated that a representative had booked an appointment with him but had failed to turn up at the appointed time. The representative had confirmed that he had been double booked by telephone after the time of the appointment expressing his inability to keep the appointment.

The complainant informed Sankyo that he wished to claim his fee of £95 from the company for his wasted time saying that this was in accordance with a previous case (Case AUTH/122/3/94) and that he was determined to see that his time was not wasted by any other medical representative in the future.

RESPONSE

Sankyo submitted that the complaint was based on a misunderstanding. It appeared that on 1 September 1997 at 2.50pm an appointment was made by one of its representatives for 10.30am on 7 October. Since the appointment was made, the representative had changed territories. The appointment was handed over to the new representative, who attended the appointment and spoke to the complainant for 10-15 minutes.

Sankyo confirmed that a telephone call was made to the surgery. The reason for the call was that the representative had difficulty in finding the surgery and needed further instructions. He arrived late, at approximately 10.45, after the receptionist had given him directions. The representative advised the surgery during this call that he would be a little late.

Sankyo could only assume that the complainant expected to see the representative who made the original appointment and instead saw the new representative. Sankyo submitted that perhaps the explanation for this change had not been made sufficiently clear to the complainant and that was why he considered the company was open to complaint.

PANEL RULING

The Panel noted that there would inevitably be a turnover of personnel in any sales force. It would not be unusual for a company representative to make an appointment to see a doctor but for another one to keep it. In such circumstances the Panel considered that companies should inform doctors of the change in personnel so as to avoid any misunderstanding.

The Panel considered that this case might be due to mistaken identity. The representative who made the appointment was not the one who turned up. There appeared to be a difference in the description of events. The complainant stated that the original representative had phoned to explain that he had been double booked whereas the company stated that the replacement representative had telephoned the surgery for directions and to advise that he would be late.

The Panel noted that the new representative had had difficulty in finding the doctor's surgery and had acted responsibly and courteously by telephoning ahead to ask for directions and to advise that he would be late. A representative of Sankyo did keep the appointment. No breach of Clauses 15.2 and 15.4 of the Code was ruled.

APPEAL BY THE COMPLAINANT

The complainant found it incredible that both Sankyo and the Authority had decided to believe the erring representative.

In the complainant's view, the Appeal Board had to

decide firstly whether the Sankyo representative actually saw the complainant on 7 October and secondly whether the complainant was particularly interested in seeing a specific Sankyo representative, (as mentioned in the Sankyo letter) and it was only because he did not come himself that actually infuriated the complainant, thus leading to the complaint and asking to be compensated for the lost time.

The complainant put forward some of the facts that were not disputed by him, Sankyo and the Authority:

1 That an appointment was requested over the phone and given to see the complainant on behalf of Sankyo at 10.30 on 7 October.

2 That the Sankyo representative did not turn up at the appointed time.

The truth was that a person calling himself [Christian name only given] had rung for an appointment for Sankyo and was given the above time and date. He also gave his telephone number.

No-one turned up at 10.30am on 7 October but at 10.37 a person from Sankyo rang saying he was given the wrong address by his colleague. This telephone call was not disputed by Sankyo but then Sankyo said in its letter that its representative arrived at the surgery at 10.45am and even talked to the complainant for 10-15 minutes. This was absolutely untrue because no-one could drive from where the telephone call was made to the surgery, a distance of 13 miles, in just 8 minutes. Nor did they know the complainant's routine as it was impossible for any representative to see him at 10.45 as he left surgery by then until the evening. However the Sankyo representative did see the complainant not on 7 October but on 24 October instead at about 5pm in the midst of a full surgery without a prior appointment to express regret for his default. The complainant stated that the representative's face was "full of guilt" and he said to the complainant "I would lose my job". The complainant told him that that he should have had the sense to ask directions to his surgery before he set off to come on 7 October and they would have been pleased to direct him. What was the use of his coming then?

The complainant stated that it must be asked where the Sankyo representative was at 10.37am on 7 October. He said over the telephone that he was at a particular location so the complainant's receptionist replied that he could no way keep his appointment. He certainly was not in the town where the surgery was situated or else they would have been kind to him and considered it a traffic congestion problem. So what was he doing 13 miles away and in another town which did not even sound a similar name as the town where the surgery was located and you asked yourself whether this representative like a headless person travelled to a wrong address foolishly without first ascertaining where he was going? And without any regard to a crucial time to reach for keeping an appointment. The complainant could only guess that he must have had some other interest, presumably to see GPs, hence the "double appointment". Certainly his intention was any other than to keep his appointment with the complainant.

Then the managing director of Sankyo stated (as did the Authority) that the complainant was very unhappy as he did not see a particular person hence the complaint. Could one believe the contradictory statements of the managing director as stated in his letter? On the one hand he said that the representative saw the complainant for 10-15 minutes on 7 October and in the same letter he said that the complainant was not happy that a particular representative did not come to see him. If that was so the complainant could have bluntly refused to see any other Sankyo representative other than the one who had made the original appointment. Sankyo did not specify any reason as to why the complainant must be longing to see this representative who the complainant had no recollection of ever seeing nor did he know him at all. This line of thinking by Sankyo appeared particularly mean and the complainant assured the company that he would have, and in the future also, welcome anyone from Sankyo but at the appointed time. And ask why did the complainant see the representative in question when he abruptly presented himself on 24 October at an odd time? In fact the receptionist on 7 October at 10.37, and as admitted by Sankyo, gave directions to the representative to reach the surgery without regard as to who he was. Therefore the company had exposed themselves to ridiculous and spineless argument/excuse.

The complainant therefore asked the Appeal Board to uphold his charges of wasted time by irresponsible Sankyo and to make the company to pay up as that would give GPs confidence in the pharmaceutical industry of prevailing justice.

RESPONSE FROM SANKYO

Sankyo took great exception to the language used by the complainant. Regarding the specifics of the complainant's letter, the complainant believed that the Appeal Board had to decide on two points:

1 Whether a Sankyo Representative saw him on 7 October or not?

Sankyo re-stated that the representative in question did attend the surgery on 7 October. Sankyo had acknowledged he was late, as its GP list did not have the correct address for the complainant. It listed the doctor as being located in another town. The representative earlier called on a retail pharmacist in the town where he thought the complainant's surgery was located, who said that there was no doctor of that name there, but that he practised in another named town. He telephoned for directions *en route*, and saw the complainant between 10.50 and 11am.

2 Whether the complainant was interested in seeing a particular Sankyo representative?

Sankyo's reason for suggesting this in its original letter was not intended to be a statement, but a question. As Sankyo was thoroughly confused by this complaint, its only conclusion was that it centred around a mix-up over identity, as a Sankyo representative did keep the appointment, albeit 20 minutes late.

There appeared to be no dispute from the complainant that a telephone call was made by a Sankyo representative to the surgery at around 10.30. The representative made the call whilst *en route* to the surgery, and was not, therefore, the full 13 miles away that represented the full distance between the two towns.

The complainant went on to state that it was untrue that he was seen by Sankyo. To justify this contention he pointed out two pieces of "evidence":

Firstly the impossibility of driving 13 miles in just 8 minutes and secondly that Sankyo did not know his routine, as he left surgery at 10.45.

Five things puzzled Sankyo about these points:

1 If the complainant believed he did not see a Sankyo representative, why did he need to use "evidence" to support it? Either he did or he didn't.

2 The 13 miles in 8 minutes was irrelevant as the complainant was not 13 miles away. He was *en route* already.

3 No GP, in Sankyo's experience, ever left by exactly the same time every day.

4 As the telephone call was not disputed, why would a Sankyo representative bother to make this call, unless they were on their way and advising of a delay, or ringing to cancel, both options describing the highly professional approach to be expected from the pharmaceutical industry.

5 During this telephone call why would the receptionist tell him that "he could no way keep his appointment" but still gave directions to reach the surgery. Surely she would only give directions if he was within a certain distance from the surgery, not 13 miles away.

The complainant discussed this call in further detail, and acknowledged that the representative had admitted to being in the wrong town. If the representative had been guilty of anything other than suffering from an incorrect address, he would hardly have been so open about his whereabouts.

Finally, regarding the face to face call by the representative with the complainant on 24 October; again, this call was not in dispute by either party. The representative called to try to discover why the complainant had complained over an appointment he had kept, and to attempt to pacify the complainant (he was not instructed to do so by the company and, incidentally, Sankyo believed that this was a misguided and unintentionally unhelpful act).

The representative denied stating he would "lose his job" and he also disputed the assertion that the surgery was full. There was only one patient in the waiting room.

Sankyo was sorry that the complainant believed that its arguments were ridiculous and spineless. Sankyo took the conduct of its representatives very seriously, and if there was any truth in the accusations Sankyo would take appropriate action.

Sankyo hoped that it had demonstrated that there were some fundamental flaws in the complainant's logic. Sankyo failed to understand his reasons for this complaint, and hoped that his faith in the pharmaceutical industry would not be irreparably damaged by this issue, whatever the ruling.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant commented on all points in the letter from Sankyo.

1 A Sankyo representative did not show up at all at the surgery on 7 October. The GP addresses list held by Sankyo might have misled its own representative to the other town but that was its problem, not the complainant's, although it was certainly blaming the complainant for it.

2 The Sankyo managing director was absolutely wrong to insist that his representative did see the complainant on 7 October because obviously the managing director was not present himself at the surgery watching the representative's arrival, the complainant was, whatever the time of the day. Be it 10.45 as the managing director said in his previous letter to 10.50 and 11am in his current letter after the complainant had pointed out the impossibility of covering the distance involved in 8 minutes.

3 The receptionist was yet another person who was referred to and who quite clearly remembered the event and had also noted the non-arrival into the practice diary and the call made by the representative from the other town at 10.37.

4 The Sankyo managing director said that he was "confused and puzzled" by the complaint. How could anyone in this state continue to defend what was absolutely untrue. The complainant hoped that once he accepted what the complainant said, then his confusion and puzzlement would fizzle away.

5 There were already attempts to close ranks, be offensive to the complainant, blinker views and shift blame on to the victim - the complainant.

6 Sankyo might have its reasons to defend its representative, but the complainant was the one who was actually kept waiting for the arrival of the representative who did not come, so the complainant suffered. Instead no-one wanted to accept this and instead Sankyo had already won on the first given occasion. This was not justice, the pharmaceutical industry was in the dock.

INITIAL APPEAL BOARD CONSIDERATION

The Appeal Board noted that the complainant had been told by the Authority that it had no jurisdiction in relation to his claim for a £95 fee for wasted time. The complainant had referred to a previous case (Case AUTH/122/3/94) where a GP in private practice had claimed £95 from a company when a representative had failed to keep an appointment. This was an issue that the complainant would have to pursue with the company himself.

The Appeal Board gave initial consideration to this case and decided that it needed more information from both parties before it could make a ruling.

The Appeal Board noted that when considering cases involving representatives it was always difficult to determine exactly what had happened. In this particular case the two versions of what had happened were quite different.

The complainant had made a serious and specific allegation about the conduct of a representative of Sankyo. The Chairman reminded the Appeal Board that Paragraph 4.7 of the Constitution and Procedure provided that where an appeal was brought which was concerned with an issue of fact between a complainant and the

company concerned which could not be properly resolved without the oral evidence of the persons directly involved, the Chairman might invite such persons to attend and give evidence.

The Appeal Board considered that as the matter was concerned with an issue of fact which could not be properly resolved without the oral evidence of the people directly involved, the Chairman should invite the complainant and the representative in question to attend the next meeting of the Appeal Board. It would be helpful if both parties were asked to bring documentary evidence to support their respective submissions.

FURTHER COMMENTS FROM THE COMPLAINANT

No further comments or evidence were received prior to the appeal. The complainant brought his practice diary to the appeal.

FURTHER COMMENTS FROM SANKYO

Sankyo submitted six documents as evidence, these being:

1 A print off from the computer screen of the main doctor database Sankyo used to record its medical representatives' calls. Sankyo submitted that this demonstrated that the doctor's address was correct except for the important aspect of the town.

2 The hard copy print out derived from all the addresses such as in 1 above, showing, again, the complainant listed as being in the incorrect brick.

3 A copy of the representative's call report, showing that he recorded a call on the complainant on 7 October, at which he sold three products.

4 A copy of the representative's call report, showing that he did not record a call on the complainant on 24 October because he did not sell any products and that would be against company policy. It would be recalled that he returned to see the complainant to try to smooth over the problem.

5 A copy of the representative's mobile telephone bill, showing a call made at 10.36am (although this call was not in dispute).

6 A personal note from the representative, which explained why Sankyo was unable to submit a letter from the pharmacy. However, there was further information in support of Sankyo's position, in respect of the dispensing of a prescription from a patient belonging to the local surgery and the timing of the journey to the complainant's surgery.

* * * * *

The complainant was provided with a copy of the further comments from Sankyo and Sankyo was shown the relevant pages of the practice diary on a strictly private and confidential basis.

The complainant and his receptionist gave their version of events to the Appeal Board. Sankyo then gave its version of events to the Appeal Board. The complainant and the receptionist appeared for a second time before the Appeal Board. Both parties were questioned by the Appeal Board.

* * * * *

APPEAL BOARD RULING

The Appeal Board noted that the original complaint was that a representative had double booked appointments and so had failed to keep his appointment with the complainant on the morning of Tuesday, 7 October 1997. The complainant had stated that the representative had confirmed his double booking by telephoning after the time of the appointment expressing an inability to keep it. The Appeal Board noted that the complainant's practice diary for the day, which had been filled in by the receptionist, had the following entry: "10.30 - [name] - Sankyo. [telephone number]" followed, in red ink, by "Cancelled at 10.37 said was in [named town]. Was given wrong address by his colleague". The telephone call had been taken by the receptionist. The complainant confirmed that he was advised of the cancelled appointment shortly after the telephone call was received and so did not wait any longer for the representative.

The Appeal Board noted that documentation provided by Sankyo showed the complainant's surgery to be in the wrong town. The surgery was in fact in another town. Sankyo also provided evidence to show that a telephone call of just over 1 minute was made to the complainant's surgery at 10.36 on 7 October 1997. The representative stated that he had tried to telephone the surgery earlier but had only got the engaged tone.

The Appeal Board noted that there were some inconsistencies as to what was actually said in the telephone conversation. The original letter of complaint said that the representative had expressed an inability to keep the appointment. The practice diary recorded that the appointment was cancelled at 10.37. The letter of appeal from the complainant said that, on hearing the whereabouts of the representative, the receptionist had told him that he could in "no way keep his appointment" but also that the receptionist "gave directions to the Sankyo man to reach the surgery". The original response from Sankyo stated that directions to the surgery had been given.

With regard to the appointment the Appeal Board noted that the complainant maintained that no representative from Sankyo had arrived on 7 October 1997. This was confirmed by the receptionist who was at the surgery all day. The receptionist described the layout of the surgery which was such that access to the doctor's consulting room was through the receptionist's office which also served as the waiting room. The Appeal Board noted that the representative had recorded on his GP call report form that he had kept his appointment with the complainant and had detailed three products. The representative stated that he did not see the doctor's receptionist that day. After seeing the complainant the representative said that he then went to another surgery and saw three doctors before seeing a fourth doctor at lunchtime. Three more telephone calls were made between 11.20 and 11.29am.

The Appeal Board noted that both parties agreed that a meeting had taken place on Friday, 24 October 1997. The Appeal Board noted that the doctor's receptionist did not work on Fridays and so the complainant was on his own at the surgery. The complainant confirmed that in such circumstances he would sit in the receptionist's office/waiting room. The Appeal Board noted that both parties agreed that the meeting had taken place in the first

available room off the entrance hall, ie the receptionist's office/waiting room although the representative described it as the doctor's consulting room. The representative said that he had seen the complainant in the same room on Tuesday, 7 October which the Appeal Board noted was a day when the receptionist was at work and would have been at her desk. On such a day the meeting would have been held in the actual consulting room which led off the office/waiting room.

Noting the representative's schedule for the morning and his description of the complainant's surgery, the Appeal Board's view was that, on the balance of probabilities, the representative had not kept his appointment with the complainant on 7 October 1997.

The Appeal Board considered that the failure of a representative to keep an appointment was not necessarily a breach of the Code. The circumstances needed to be taken into account.

The Appeal Board noted that when the representative became aware that he had incorrect information about the location of the surgery, he had endeavoured to contact the surgery. It was unfortunate that the representative had not been able to contact the surgery prior to the time of the appointment, 10.30, but the line had been engaged. Following the telephone call from the representative at 10.36 the complainant knew that the appointment had been cancelled. The practice diary recorded both that the appointment had been cancelled and the time of the call, 10.37. The Appeal Board considered that the representative had acted appropriately in telephoning the surgery as quickly as he could once he realised that the surgery was in the other town. It was unfortunate that the complainant had been kept waiting a few minutes before receiving the information about the representative's telephone call but the Appeal Board considered that this was not a breach of the Code. The Appeal Board therefore upheld the Panel's rulings of no breach of Clauses 15.2 and 15.4 of the Code.

The complainant's appeal therefore failed.

The Appeal Board considered that other issues which arose from the representative's conduct on 7 October 1997 were internal matters for Sankyo.

Complaint received **21 October 1997**

Case completed **25 February 1998**

CASE AUTH/631/10/97

JANSSEN-CILAG v LUNDBECK

Promotion of Serdolect

Janssen-Cilag complained about a bar chart used in the promotion of Serdolect by Lundbeck. The bar chart addressed the issue of extrapyramidal symptoms (EPS) as a side effect of antipsychotic medicines. The three sets of results shown on the bar chart were from placebo referenced studies between Serdolect and haloperidol, olanzapine and haloperidol, and risperidone (Janssen-Cilag's product Risperdal) and haloperidol. Janssen-Cilag stated that the visual presentation was clearly intended to lead the reader to conclude that Serdolect had less propensity to cause EPS than either risperidone or olanzapine, a fact which Janssen-Cilag would dispute and which Lundbeck could not substantiate as there was no direct comparative trial between Serdolect and either risperidone or olanzapine. Janssen-Cilag alleged that the presentation of three separate results on the one page misled the reader to conclude that Serdolect induced less EPS than risperidone.

The Panel noted that although the bar chart showed three separate sets of data it was essentially one bar chart. The atypical antipsychotics, Serdolect, olanzapine and risperidone, had each been compared with haloperidol in three separate studies but had not been compared with each other. In the Panel's view the bar chart visually implied an advantage for Serdolect which had not been shown as there had been no direct comparisons of Serdolect with either olanzapine or risperidone. The Panel considered that the bar chart was misleading and it was ruled in breach.

Upon appeal by Lundbeck, the Appeal Board's view was that the bar chart visually implied an advantage for Serdolect which had not been shown as there had been no direct comparisons for Serdolect with either olanzapine or risperidone. The Appeal Board considered that the bar chart was misleading and upheld the Panel's ruling that the Code had been breached.

Janssen-Cilag Ltd complained about a bar chart used in the promotion of Serdolect by Lundbeck Limited. Lundbeck, although not a member of the ABPI, had nevertheless agreed to comply with the Code. The bar chart addressed the issue of extrapyramidal symptoms (EPS) as a side effect of antipsychotic medicines. The bar chart had appeared in a leavepiece (DCA/525/105) and a product summary booklet (DCA/525/109). The bar chart in the leavepiece appeared on a page headed "Placebo-level EPS" and was entitled "Illustration of percentage of patients using anti-EPS medication in 3 different placebo referenced studies". The bar chart in the product summary booklet appeared on a page headed "Use of anti-EPS medication" and was entitled "Percentage of patients using anti-EPS medication in three different studies". The x axis of both charts was labelled with the names of the medicines and doses while the y axis plotted "Percentage difference from placebo" (-10% - +60%).

The three sets of results shown on the bar chart were from placebo-referenced studies between Serdolect and haloperidol, olanzapine and haloperidol, and risperidone and haloperidol. Data from each study was separated from the data from the other two studies. Results were highlighted if a significant difference versus placebo or versus an equiefficacious dose of Serdolect had been shown. Data from the Serdolect study showed that Serdolect (12-24mg) was little different from placebo in terms of the number of patients requiring anti-EPS medication while significantly more patients on haloperidol (4mg, 8mg and 16mg) than on placebo required anti-EPS medication. Data from the second study showed that while some patients needed anti-EPS medication on olanzapine (6.6-16.3mg) statistically the percentage was no different to placebo. Conversely, compared with placebo, haloperidol 16.4mg showed a marked increase in anti-EPS medication needed. In the final study risperidone (2-10mg/day) showed no statistical difference to placebo while a dose of 16mg was associated with significantly more anti-EPS medication than placebo as was 20mg of haloperidol. In almost all cases the bars for olanzapine and risperidone showed that, although statistically no different to placebo, more patients used anti-EPS medication than the patients taking Serdolect.

Beneath the bar chart in the leavepiece was the statement "The low incidence of extrapyramidal symptoms (comparable to that of placebo) in clinical studies indicates that Serdolect may have less potential than classical antipsychotics to induce tardive dyskinesia. It has been shown that EPS during antipsychotic therapy is linked to subsequent development of tardive dyskinesia". The claims made for Serdolect in association with the bar chart in the product summary booklet were "The use of anti-EPS medication is indistinguishable between Serdolect at any dose and placebo" and "No evidence of a dose-response effect on EPS or use of anti-EPS medication was observed for Serdolect".

COMPLAINT

Janssen-Cilag stated that the visual presentation was clearly intended to lead the reader to conclude that Serdolect had less propensity to cause EPS than either risperidone or olanzapine, a fact which the company would dispute and which Lundbeck could not possibly substantiate as there was no direct comparative trial between Serdolect and either risperidone or olanzapine.

Janssen-Cilag alleged that the presentation of these separate studies results on the one page therefore misled the reader to conclude that Serdolect induced less EPS than Risperdal. Janssen-Cilag alleged that the detail aid and the product summary booklet were in breach of Clause 7.2.

RESPONSE

Lundbeck said that the product summary was a brief overview of the product and was designed to be left with clinicians and pharmacists by the representative for future reference. The extrapyramidal side effects leavepiece was left with those clinicians and pharmacists who expressed an interest in the EPS profile of sertindole.

Lundbeck submitted that the three studies were illustrated in the product summary and the leavepiece to put the low potential for extrapyramidal symptoms demonstrated for the atypical antipsychotic, sertindole, in context with the results from two studies of similar design involving the atypical antipsychotics olanzapine and risperidone. The inclusion of these studies also illustrated the consistently higher incidence of EPS with the typical antipsychotic, haloperidol.

Lundbeck submitted that it was stated clearly in the text above the bar chart in both pieces that the data presented came from three different studies. Data from these three studies were presented separately and clear references to the studies were given beneath each set of data. In addition to a reference, a short description of the study with the number of patients enrolled and the treatment period was given under each set of data, which emphasised still further the fact that these were different studies.

Clear references to statistically significant differences to placebo were given. No dose of sertindole, or olanzapine or risperidone up to 10mg per day gave rise to a significantly different proportion of patients needing anti-EPS medication from those who received placebo. Therefore, sertindole was no different from either olanzapine or risperidone in this respect. Risperidone at 16mg per day did result in significantly more patients needing anti-EPS medication than those on placebo, but this was reported in the referenced study (Marder *et al*). The EPS potential of risperidone at doses above 10mg per day was also addressed in the Risperdal SPC.

Lundbeck submitted that the comparative statement accompanying this data in the product summary involved sertindole and placebo, while the comparative statement in the leavepiece involved sertindole and classical antipsychotics. Both these statements were supported by the referenced studies. In neither piece was a comparative claim made involving either olanzapine or risperidone.

Lundbeck considered that neither piece misled and the data presented were both accurate and fair.

PANEL RULING

The Panel noted that although the bar chart showed three separate sets of data it was essentially one bar chart. The atypical antipsychotics, Serdolect, olanzapine and risperidone, had all been compared in three separate studies with haloperidol but none had been compared with each other.

The Panel noted that the statement in the leavepiece compared the low incidence of EPS seen with Serdolect with that seen with classical antipsychotics. The Panel noted that the two claims associated with the bar chart in the product summary booklet were "The use of anti-EPS medication is indistinguishable between Serdolect at any dose and placebo" and "No evidence of a dose-response effect on EPS or use of anti-EPS medication was observed for Serdolect". No claims or comparisons were made regarding olanzapine or risperidone. The only data regarding these two atypical antipsychotics was presented in the bar chart.

The Panel noted that in both the product summary booklet and the leavepiece the bar chart occupied almost all of one page. The Panel considered that the visual impact of the bar chart was such as to invite readers to favourably compare the percentage of Serdolect treated patients using anti-EPS medication with the percentage of olanzapine and risperidone treated patients needing anti-EPS medication.

In addition, the Panel considered that readers might read the two claims, "The use of anti-EPS medication is indistinguishable between Serdolect at any dose and placebo" and "No evidence of a dose-response effect on EPS or use of anti-EPS medication was observed for Serdolect", associated with the bar chart in the product summary booklet and favourably compare Serdolect with olanzapine and risperidone.

In the Panel's view, the bar chart visually implied an advantage for Serdolect which had not been shown as there had been no direct comparisons of Serdolect with either olanzapine or risperidone. The Panel considered that the bar chart was misleading and ruled a breach of Clause 7.2 of the Code. This applied to both the leavepiece and the product summary.

APPEAL BY LUNDBECK

Lundbeck emphasised that the three studies illustrated in the product summary and the leavepiece were intended to put the low potential for extrapyramidal symptoms demonstrated for the atypical antipsychotic, sertindole, in context with the results from two studies of similar design involving the atypical antipsychotics olanzapine and risperidone. The inclusion of these studies also illustrated the consistently higher incidence of EPS with the typical antipsychotic, haloperidol.

The fact that these were three different studies was stated clearly in the text above the bar chart in both pieces. Data from these three studies were presented separately and clear references to the studies were given beneath each set of data. In addition to a reference, a short description of the study with the number of patients enrolled and the treatment period was given under each set of data which emphasised still further the fact that these were different studies.

Clear references to statistically significant differences to placebo were given. No dose of sertindole, or olanzapine or risperidone up to 10mg per day gave rise to a significantly different proportion of patients needing anti-EPS medication from those who received placebo. Therefore, sertindole was no different from either olanzapine or risperidone in this respect. Risperidone at 16mg per day did result in significantly more patients needing anti-EPS medication than those on placebo, but this was reported in the referenced study. The EPS potential of risperidone at doses above 10mg per day was also addressed in the Risperdal summary of product characteristics.

The comparative statement accompanying this data in the product summary involved sertindole and placebo, while the comparative statement in the leavepiece involved sertindole and classical antipsychotics. Both these statements were supported by the referenced studies. In neither piece was a comparative claim made involving either olanzapine or risperidone. In both cases it was intended to show the advantages demonstrated in clinical

studies for sertindole over haloperidol. Lundbeck did not believe that unfair advantages over olanzapine or risperidone were implied.

Lundbeck continued to believe neither piece misled and that the data presented were both accurate and fair.

APPEAL BOARD RULING

The Appeal Board noted that the data presented in the leavepiece and the product summary booklet had come from three separate studies. Only one study had compared Serdolect and haloperidol. The other two studies had compared olanzapine and haloperidol and risperidone and haloperidol. The Appeal Board considered that the presentation of the data invited readers to make comparisons between all three studies and favourably compare Serdolect with both olanzapine and risperidone.

In the Appeal Board's view the bar chart visually implied an advantage for Serdolect which had not been shown as there had been no direct comparisons for Serdolect with either olanzapine or risperidone. The Appeal Board considered that the bar chart was misleading and upheld the Panel's ruling of a breach of Clause 7.2 of the Code.

The respondent's appeal therefore failed.

Complaint received 27 October 1997

Case completed 4 March 1998

CASE AUTH/632/10/97

DIRECTOR/MEDIA v GLAXO WELLCOME

Meeting in Dublin

A letter published in The Daily Telegraph was critical of an all-expenses paid weekend in Dublin arranged by Allen & Hanburys to which the author of the letter, a doctor, had been invited. There would be seven and a half hours of lectures and discussions and he could see no valid excuse for such conferences which he felt could be held much more cheaply closer to home.

The Panel noted that the Code did not prevent companies from holding meetings at venues outside the UK but the impression created by the arrangements had to be kept in mind. The programme should attract the delegates not the venue. The Panel queried why the meeting had been held in Dublin given that the delegates and most of the speakers came from three regions of the UK relatively close to one another. The meeting could have been held at a convenient location in the UK. The Panel considered that the cost of the meeting was more than the level which those attending would normally adopt if paying for themselves. The arrangements for the meeting were unacceptable and were ruled in breach. The Panel considered that the educational content was not unreasonable and no breach of the Code was ruled in that regard.

Upon appeal by Glaxo Wellcome, the Appeal Board noted that all the circumstances had to be considered, including cost, location, the educational content, the level of associated hospitality and the overall impression created by the arrangements. Pleasant venues could be used but the programme should attract delegates, not the venue. In the Appeal Board's view it was difficult for companies to justify holding meetings for UK health professionals at venues outside the UK. Attendance at an international scientific congress would be one exception to this.

The Appeal Board considered that the cost per head exceeded that which the delegates would usually adopt when paying for themselves and that the meeting could have been held at a convenient location in England. There was no valid reason for having it in Dublin. The Appeal Board considered that overall the arrangements for the meeting were unacceptable and upheld the Panel's ruling that the Code had been breached.

A letter, written by a doctor, headed "Drugs prescribed far too often" and published in The Daily Telegraph on 25 October 1997 criticised Allen & Hanburys for arranging an all-expenses paid weekend in Dublin. The matter was taken up with the parent company, Glaxo Wellcome UK Limited, as a complaint under the Code with the Director acting as the complainant in accordance with the usual practice.

COMPLAINT

The author of the letter stated that the pressure on GPs to prescribe was enormous and that this was both patient and pharmaceutical company driven. The author further stated that pharmaceutical companies' methods of advising patients of the availability of expensive new medicines in newspapers and magazine articles, combined with continually raising patient expectations by similar means, contributed significantly. The author stated that he had been invited by Allen & Hanburys for an all-expenses paid weekend in Dublin for seven and a half hours of lectures and discussion. The author could see no valid excuse for such conferences which he felt could be held much more cheaply closer to home.

RESPONSE

Glaxo Wellcome stated that the meeting, arranged for the weekend of 21-23 November 1997, was designed to bring together doctors from hospitals and primary care to discuss topics in respiratory medicine. Most of the programme was dedicated to the recognition and management of chronic obstructive pulmonary disease (COPD) and there were parallel sessions for hospital doctors and general practitioners, and combined sessions where the two groups could discuss issues of mutual concern. The programme had been put together with considerable thought. The speakers were mostly from the UK and they were respected in their own fields. One

speaker was a respiratory specialist in Dublin who had carried out research into the mechanisms of "cough" and its investigation. Glaxo Wellcome provided a copy of the draft programme and confirmed the names and positions of the speakers.

Doctors from the West Midlands, Wessex and the south west of England had been invited to attend this meeting. It was planned for 40 delegates from primary and secondary care who would have received their invitations from their local Allen & Hanburys representatives. There were meetings "closer to home", which were usually held in the evening. While they were of high educational value, they could not address issues in the depth that was possible at a meeting such as the one held in Dublin. Seven and a half hours was quoted dismissively but the programme was quite intensive.

Glaxo Wellcome stated that the Saturday session ran from 9am to 3pm with breaks only for coffee and lunch. The Sunday session ran from 9am until 12noon, when lunch would be taken, following which the delegates would return to their homes. Bearing in mind that the doctors who were attending this meeting would have worked a full week in the week preceding and would be returning to work the following day, Glaxo Wellcome submitted that a short break for relaxation on the Saturday afternoon, from 3pm onwards, did not seem unreasonable.

In terms of what was included, the delegates arrived at Dublin Airport on Friday afternoon and were transferred to the Hotel Shelbourne in Dublin. That evening there would be a half-hour drinks reception followed by dinner in the hotel. On the Saturday night, dinner would be taken at the Grey Door Restaurant in Dublin. No other activities had been arranged and all personal extras were the responsibility of each delegate; for example, newspapers, telephone calls and drinks taken in their own bedrooms. Glaxo Wellcome confirmed that the anticipated cost of this meeting, assuming a minimum of 40 delegates, was estimated at £720 per delegate, which would include cost of flight, hotel transfer, accommodation, meeting rooms, meals and insurance for all of the delegates attending. Hotel and restaurant costs in Dublin were similar to those in the UK for a comparable standard of accommodation. For most of the delegates the time taken for flights to Dublin would certainly be less than travelling to a single venue within the extensive areas of England from which they came. Inevitably it might be convenient for some to be near to home, but for many it would involve several hours of driving. It should be noted that flights to Dublin were from the regional airports at Birmingham, Bristol and Bournemouth to minimise the time spent for any of the delegates in travelling.

Glaxo Wellcome stated that there had been acceptances from 26 delegates who would be accompanied by the speakers, 5 representatives from Allen & Hanburys and a regional medical advisor with Allen & Hanburys who had played an important role in planning the meeting.

Allen & Hanburys, as a part of Glaxo Wellcome UK Limited, had always taken considerable pride in the quality of its educational meetings and the forthcoming meeting in Dublin was no exception. The programme for the meeting was of high quality and the level of hospitality was appropriate to the meeting, to the group of doctors who would be attending, and was secondary to the nature of the meeting itself. Glaxo Wellcome submitted that this meeting was not in breach of Clause 19 nor, by implication, of any guidelines for doctors which had been drawn up by the General Medical Council.

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 delegates would fly to Dublin from one of three regional airports, Bristol, Birmingham or Bournemouth. Doctors in the West Midlands, Wessex and the south west of England had been invited to attend the meeting. The educational part commenced on the Saturday morning at 9am and finished at 3pm with breaks for coffee and lunch. This was followed by a session on Sunday morning which commenced at 9am and finished at midday with a break for coffee. The Panel considered that the educational content of the meeting was not unreasonable.

The Panel queried why the meeting had been held in Dublin given that the delegates and most of the speakers came from only three regions of the UK, ie the West Midlands, Wessex and the south west of England. The Panel noted that these three regions were relatively close to one another. The Panel considered that the meeting could have been held at a convenient location in England and this would not necessarily have increased the overall travelling time. The Panel noted that the cost of the meeting had been estimated at £720 per delegate if 40 delegates had attended. It considered that this was more than the level that 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 considered that as the educational content was not unreasonable there was no breach of either Clauses 2 or 9.1 of the Code and ruled accordingly.

APPEAL BY GLAXO WELLCOME

Glaxo Wellcome said that when its original response to the complaint was prepared, which was before the meeting had actually taken place, the cost of the meeting had been estimated at £720 per delegate inclusive of room and equipment hire, but exclusive of any personal extras. The Shelbourne Hotel in Dublin was a comfortable, 4-star hotel which did not have any leisure facilities. Glaxo Wellcome considered that it was the type of hotel which would provide a suitable setting for an interactive

weekend educational programme and one at which the delegates, consultant physicians and general practitioners, would choose to stay, and the costs of which did not exceed the level which the attendees would normally pay for themselves.

Now that the meeting had taken place, the cost per capita for 51 delegates was £625.38. A breakdown of the mean costs was provided which covered two nights' bed and breakfast, with lunches, coffees and dinner at the hotel, room rental, dinner at the Grey Door Restaurant, together with economy return flights to Dublin and personal insurance. It should be noted that the programme included virtually no time for free activity. The final programme was identical to the draft programme provided to the Panel.

The company's representative confirmed that these costs were mean figures and the cost of room rental was included in the cost of lunch and coffee over the two days.

Glaxo Wellcome still believed that this cost was not excessive and was within the range that doctors such as these might personally choose to spend for a weekend at a comfortable hotel. It was unrealistic to compare these prices with those for a "bargain break" type of weekend. Fifty-one delegates stayed in a hotel appropriate to their position, but no more, which could provide the facilities necessary for presentations and discussions in both plenary and syndicate sessions.

While Glaxo Wellcome noted the Panel's comment that the delegates came from only three regions, namely the West Midlands, Wessex and the south west of England, it was worth noting that Stoke-on-Trent, in the north, was 240 miles from Plymouth, in the west, for example, and 180 miles from Southampton, in the south. The company's representative confirmed that these three regions constituted one of Glaxo Wellcome's sales regions and that the majority of the delegates came from the West Midlands.

Glaxo Wellcome had had a similar hypothetical meeting costed for a suitable 4-star hotel in Bath, which was close to the centre of this regional triangle. The price of such a meeting would be £500 for each delegate. The cost for bed and breakfast would be £130.50 per person per night and Glaxo Wellcome had calculated a weighted and average return first class rail fare of £70 for the same delegates to attend. The cost of room hire at the hotel in Bath would be greater by a few hundred pounds, divided across the delegates. The company's representative confirmed that Glaxo Wellcome had been able to negotiate a special package deal with the Bath hotel whereby dinner at the hotel on Friday night was provided free of charge but the company would have to pay for drinks to accompany dinner.

Glaxo Wellcome appreciated that the Dublin meeting was slightly more expensive but it felt that a direct flight to Dublin was more relaxing and more acceptable at the end of a busy week compared with the prospect of rail travel and the need to make connections between trains. This would likely put the delegates at greater ease making them more able to benefit from the education provided at the meeting. The sum was not substantial in these circumstances. If delegates chose to drive, in Glaxo Wellcome's hypothetical case, then this would involve driving 140 miles from Stoke-on-Trent, which would take at least 4-5 hours on a Friday evening. The company's representative provided a table of approximate comparative travel times from the regions in question to Bath and Dublin.

Glaxo Wellcome stated that if it had held a meeting for doctors from a smaller area than the catchment area for this meeting then the venue would be more local and convenient to that area.

The company referred to a number of previous cases which were relevant to the Appeal Board's consideration of the present case.

In conclusion, while Glaxo Wellcome accepted that it was slightly more expensive to hold the meeting in Dublin it still considered that the delegates were better able to obtain greatest benefit from the meeting than would have been the case if they had driven the greater distances by road or travelled by rail to a centre which was arbitrarily more central for the three regions concerned. The feedback from the delegates had been very good both in terms of the programme, the speakers and for providing a forum for consultants and general practitioners to discuss the same topics together.

Glaxo Wellcome believed that this was a meeting of high educational value, which demanded an active contribution from the delegates. The hospitality was appropriate to the meeting and to the delegates who attended. The company believed it was not excessive and was at the level that these doctors were likely to have provided for themselves.

APPEAL BOARD RULING

The Appeal Board noted that when considering whether a meeting and associated hospitality contravened Clause 19.1 of the Code all the circumstances had to be considered, including cost, location, the educational content, the level of associated hospitality and the overall impression created by such arrangements. Each case had to be considered on its own merits.

The Appeal Board noted that the Code did not prevent companies from holding meetings for UK health professionals at venues outside the UK but considered that there had to be valid and cogent reasons for so doing. The impression created by the arrangements for any meeting must be kept in mind. The Appeal Board considered that while it was acceptable for companies to hold meetings at pleasant venues, it should be the programme that attracted delegates and not the venue. In the Appeal Board's view it was difficult for companies to justify holding meetings for UK health professionals at venues outside the UK. Attendance at an international scientific congress would be one exception to this.

The Appeal Board was critical that the letter of invitation for the meeting was headed "The Shelbourne Hotel, Dublin 21-23 November 1997". This immediately gave the impression that delegates were being attracted by the venue and not the educational content of the meeting. The Appeal Board noted that the opening sentence of the letter referred to a respiratory weekend as did the heading to the reply form. The Appeal Board considered that the cost of the meeting, at £625.38 per head, exceeded the level which the delegates would normally adopt when paying for themselves. The Appeal Board's view was that The

Shelbourne was the best hotel in Dublin. The Appeal Board noted Glaxo Wellcome's submission regarding travelling times and distance but considered that the meeting could have been held at a convenient location in England and this would not necessarily have increased overall travelling time for the group as a whole. The Appeal Board noted that the majority of delegates were from the West Midlands. The Appeal Board considered that there was no valid reason for holding the meeting in Dublin as all the delegates and all but one of the speakers were from the UK.

The Appeal Board considered that overall the arrangements for the meeting were unacceptable and upheld the Panel's ruling of a breach of Clause 19.1 of the Code.

The respondent's appeal therefore failed.

Proceedings commenced **27 October 1997**

Case completed **24 February 1998**

CASE AUTH/634/10/97

BOEHRINGER INGELHEIM v GLAXO WELLCOME

Promotion of Serevent

Boehringer Ingelheim alleged that the claim "Use Serevent to replace q.d.s. ipratropium bromide" was medically unsound, had not been substantiated in clinical studies and was not a licensed use of Serevent. The use of Serevent in COPD was not disputed but there was no clinical data to recommend substitution of Boehringer Ingelheim's product ipratropium with Serevent in those patients who were receiving and responding to ipratropium. The Panel noted that both products were licensed for use in COPD and given the clinical data considered it reasonable that a doctor with a patient who had reached stage 2 of the disease might choose to prescribe either. There was no clinical data to suggest that patients on one would benefit from a switch to the other. The Panel considered that the claim was ambiguous as it could mean that doctors could choose Serevent instead of ipratropium when initiating therapy or it could mean that doctors should switch patients well controlled on ipratropium. The Panel considered that some doctors would read the claim to mean the latter. This was misleading and there was no data to support such an interpretation. A breach of the Code was ruled. The Panel did not consider that the claim promoted Serevent for an unlicensed indication.

In relation to the claim "It [Serevent] has been shown ... to give COPD patients a significantly greater improvement in lung function, and with a longer duration of action, than ipratropium bromide", Boehringer Ingelheim said that it was based on single dose studies and, in a chronic progressive disease like COPD, a single measurement of FEV_1 was not a strong prediction of long term efficacy. It was misleading to make the claim on that basis. Furthermore, it was recognised that the full response to ipratropium in COPD patients was not achieved until after several weeks of treatment. The Panel considered that many of the intended audience would assume that the claim and the referenced study related to long term therapy. To use data from a single dose study to support what would be assumed to be a clinical claim relating to chronic use was misleading and a breach of the Code was ruled. The Panel noted that that part of the claim relating to longer duration of action of Serevent had been substantiated. The part of the claim relating to lung function had not and was ruled in breach.

Finally, Boehringer Ingelheim referred to the claim "Compared with ipratropium ... Serevent gives COPD patients a significantly greater improvement in mean morning peak flow ... ($p<0.001$)" stating that Glaxo Wellcome in correspondence had referred to "small differences in baseline morning peak expiratory flows". These small changes in peak flow indicated a slight decrease in large airway resistance. Symptomatic improvement in these patients was unlikely to be due to changes in the large airways but to changes in the small airways and lung volumes. Although statistically significant, these changes were clinically irrelevant. The Panel considered that the claim was factually accurate and supported by the data. It highlighted a measurement which the Panel considered the intended audience was likely to understand and be able to relate to clinical practice. The Panel considered that much was being made of one measurement from a study when overall the study results had been more equitable. On balance, however, the Panel did not consider that the claim was misleading and no breach of the Code was ruled.

Boehringer Ingelheim Limited complained about the promotion of Serevent (salmeterol) for chronic obstructive pulmonary disease (COPD) by Glaxo Wellcome UK Limited. Serevent was licensed for use in COPD in July 1996.

Boehringer Ingelheim referred to two promotional items HM4159 - BP/June 1997 and 20091385 - Alp/June 1997. Glaxo Wellcome provided a detail aid (20091385 - Alp/June 1997) and a "Dear Practice Nurse" mailing which consisted of a 4 page document (HM4158 - BP/June 1997) and a "No Smoking" card (HM4161 - BP/June 1997).

1 Claim "Use Serevent to replace q.d.s. ipratropium bromide"

This claim appeared beneath the heading "When to use Serevent" in the detail aid and the "Dear Practice Nurse" document. The claim appeared beneath the heading "When to use Serevent in COPD" in the "No Smoking" card.

COMPLAINT

Boehringer Ingelheim stated that no specific reference was given in support of this claim nor was it included in the "Uses" section of the published prescribing information.

Boehringer Ingelheim stated that the use of Serevent in COPD as a long-acting ß-agonist was not in dispute. Its long duration of action would appear to be an advantage for use in chronic treatment. However, there were no clinical data to recommend substitution of Boehringer Ingelheim's product ipratropium with Serevent in those patients who were receiving and responding to ipratropium. In order to support such a recommendation it would be necessary to demonstrate that patients, who were successfully managed on ipratropium alone, benefited equally from a switch to salmeterol.

Boehringer Ingelheim stated that the study cited by Glaxo Wellcome in its response to Boehringer Ingelheim's initial complaint concerned a 12-week comparison of two groups of COPD patients, one receiving ipratropium and one salmeterol. The clinical response in both groups was essentially the same, indicating that either agent could be chosen as initial monotherapy in COPD patients. The study did not, however, permit the conclusion that salmeterol could be substituted for ipratropium in a patient satisfactorily controlled on the latter.

In addition, Boehringer Ingelheim said that ipratropium was frequently administered concurrently with a ß-agonist such as salbutamol. The substitution of ipratropium with salmeterol in such patients would lead to the patients taking a short-acting and a long-acting ß-agonist. The therapeutic benefit of such a combination in COPD did not appear to have been fully studied but might well increase the frequency of side effects and

possibly the number of daily episodes of oxygen desaturation and would certainly not be recommended practice.

Boehringer Ingelheim alleged that the claim, "Use Serevent to replace q.d.s. ipratropium bromide" was medically unsound, had not been substantiated in clinical studies, was not a licensed use for Serevent and was therefore in breach of Clauses 3.2, 7.2 and 7.3 of the Code.

RESPONSE

Glaxo Wellcome pointed out that, as stated in previous correspondence with Boehringer Ingelheim, Serevent was indicated for the treatment of COPD in patients requiring long-term regular bronchodilator therapy. This indication was similar to that at Step 2 of "Step-by-step pharmacologic therapy for COPD" in Table 4 of the American Thoracic Society's (ATS) COPD Guidelines. When published in 1995, the Guidelines proposed regular ipratropium every 6-8 hours at this step, by virtue of its slower onset and longer duration of action than the inhaled short-acting $ß_2$-agonists. Glaxo Wellcome submitted that Serevent would now logically occupy this position in patients with continuing symptoms who required regular bronchodilator therapy. Serevent also had the advantage, as far as patients were concerned, that it only needed to be administered twice daily and improvements in lung function were maintained throughout 24 hours.

Glaxo Wellcome said that it was recognised that with inhaled therapy compliance was less when a regimen required more than twice daily dosing (Tashkin (1995)). Indeed, an article by Libretto and Arbe (1997), the latter a senior medical advisor at Boehringer Ingelheim, stated that compliance was often poor and varied from 15-80% and simplicity of the treatment schedule was positively associated with higher rates of compliance.

Glaxo Wellcome said that the study which it cited in previous correspondence with Boehringer Ingelheim, was a 12-week randomised, double-blind, double-dummy, parallel group, placebo controlled comparison of the effects of salmeterol 50mcg twice daily with ipratropium 40mcg qds (the licensed doses) in 813 patients with moderate/severe COPD. In this study, changes in most outcome variables were comparable but some were significantly in favour of salmeterol, such as nocturnal breathlessness, mean morning peak expiratory flow and the premedication morning forced expiratory volume in one second (FEV_1) on the study days at the ends of weeks 4, 8 and 12 of the study. Glaxo Wellcome submitted that these results indicated that salmeterol 50mcg twice daily was likely to be at least as effective as ipratropium 40mcg four times daily in the treatment of patients with COPD.

Glaxo Wellcome said that its recommendation in the promotional items was to prescribe (ie "use") Serevent twice daily, at the equivalent of Step 2 of the ATS COPD Guidelines, instead of ipratropium taken four times daily, primarily when making a first decision at that step but also in patients in whom compliance, for example, was a problem. The company considered that doctors were unlikely to change patients to an alternative therapy when the patient's symptoms were well controlled on their existing therapy and there were no other problems.

Glaxo Wellcome considered that in this context the claim "Use Serevent to replace q.d.s. ipratropium bromide" was a reasonable claim which was consistent with the Serevent summary of product characteristics (SPC) and was not in breach of Clause 3.2 of the Code. The company did not consider that the claim was in breach of Clauses 7.2 and 7.3 as the recommendation that Serevent 50mcg twice daily was an alternative to ipratropium 40mcg qds in COPD patients was supported by the evidence provided.

PANEL RULING

The Panel noted that both ipratropium and Serevent were licenced for use in COPD. Clinical data on file from Allen & Hanburys described a parallel group study which showed that Serevent was at least as effective as ipratropium in the treatment of patients with moderate/severe COPD. The Panel noted that the 1995 ATS COPD Guidelines included ipratropium at step 2 in Table 4 which detailed the step by step pharmacological outpatient management of COPD. Serevent was not licenced for COPD until 1996. Given the clinical data, however, the Panel considered it reasonable that a doctor, faced with a COPD patient who had just reached stage 2 of the disease, might choose to prescribe either ipratropium or Serevent.

The Panel noted that there were no clinical data to show that patients either on Serevent or ipratropium might benefit from a switch of therapy to the alternative agent.

The Panel considered that the claim "Use Serevent to replace q.d.s. ipratropium bromide" was ambiguous. It was not clear whether it meant that doctors should choose Serevent instead of ipratropium when they were initiating therapy or whether it meant that doctors should switch patients well controlled on ipratropium to Serevent. The Panel considered that some doctors would read the claim to mean the latter and this was misleading. Further there was no data to support such an interpretation. The Panel therefore ruled breaches of Clauses 7.2 and 7.3 of the Code.

The Panel did not consider that the claim promoted Serevent for an unlicenced indication. No breach of Clause 3.2 was ruled.

2 Claim "It [Serevent] has been shown ... to give COPD patients a significantly greater improvement in lung-function, and with a longer duration of action, than ipratropium bromide".

Boehringer Ingelheim stated that the claim appeared in a detail aid (HM4230 - BP/June 1997). The Panel could only find the claim in a second "Dear Practice Nurse" document supplied as a photocopy by Boehringer Ingelheim with the complaint. It was not possible to read the print reference number on the photocopy. The claim was referenced to a study by Matera *et al* (1996).

COMPLAINT

Boehringer Ingelheim stated that the claim was based on single dose studies. In a chronic progressive disease like COPD a single measurement of FEV_1 was not a strong predictor of long-term efficacy. It was therefore misleading to claim that Serevent provided a significantly

greater improvement in lung function for COPD patients on the basis of single dose studies, particularly when this was not made clear in the advertising or references. Furthermore, it was recognised that the full response to ipratropium in COPD patients was not achieved until after several weeks of treatment (Rennard (1996), Bone (1994)) and therefore any comparative claim must be based on long-term studies. A comparative claim of efficacy in COPD would be extremely difficult if not impossible to substantiate.

Boehringer Ingelheim alleged that the claim that Serevent had been shown "to give COPD patients a significantly greater improvement in lung function, and with longer duration of action, than ipratropium bromide", was misleading and had not been substantiated in breach of Clauses 7.2 and 7.3 of the Code. Boehringer Ingelheim stated that in previous correspondence with Glaxo Wellcome, the company conceded that the claim could be misinterpreted, but offered neither withdrawal nor rephrasing of the claim.

RESPONSE

Glaxo Wellcome submitted that the claim was factually correct. The combination of "a significantly greater improvement in lung function" and a "longer duration of action" came from single dose studies comparing salmeterol and ipratropium. Matera *et al* (1996) studied 12 male patients with COPD using a study design similar to some of the studies quoted by Boehringer Ingelheim in an overview on COPD which had accompanied the complaint. In the Matera study, on separate non-consecutive days single doses of either salmeterol 50mcg and placebo, ipratropium 40mcg and placebo, salmeterol 50mcg and ipratropium 40mcg or two doses of placebo were administered. The results were expressed as percentage change from baseline FEV_1 against time from inhalation. The duration of action of salmeterol was significantly greater than ipratropium and the resultant improvement in FEV_1, as measured by area-under-the-curve was also greater. The peak improvements in FEV_1 were not significantly different and the combination of ipratropium and salmeterol produced no greater improvement than salmeterol alone. A study by Matera *et al* (1995) provided similar results.

Glaxo Wellcome stated that single dose studies had value but also had limitations. Single measurement of FEV_1 in an individual patient was not necessarily a predictor of whether that therapy would be effective when used regularly. This appeared to be due largely to variation in vagal tone both within and between days. In a study such as the one by Matera *et al* (1996), these variations in vagal tone would randomly affect subjects in the study but on different days, so it was unlikely that this in itself would mask changes in the group's mean values.

Glaxo Wellcome stated that the claim regarding duration of effect was supported by the study comparing placebo, salmeterol 50mcg twice daily and ipratropium 40mcg qds in 813 patients with moderate/severe COPD (data on file). In this study, the pretreatment morning FEV_1 was maintained at a significantly higher level in the patients taking Serevent compared with those taking placebo and ipratropium. Also, during the 12 hour study days on day one, and at 4, 8 and 12 weeks of the study, the effect of Serevent on FEV_1 was significantly greater than that of ipratropium at 4 to 6 hours after inhalation, as the effect of the ipratropium wore off before its next regular dose was taken.

Glaxo Wellcome pointed out that in its previous correspondence with Boehringer Ingelheim it had stated that "It may be possible for this statement to be misinterpreted", and contrary to the assertion in Boehringer Ingelheim's complaint, Glaxo Wellcome stated that it would be willing to clarify the statement further in subsequent promotional materials.

Glaxo Wellcome did not consider that the claim "[Serevent] has been shown to give COPD patients a significantly greater improvement in lung function and with a longer duration of action than ipratropium bromide" was misleading, nor that it could not be substantiated.

PANEL RULING

The Panel noted that it was an accepted principle under the Code that claims for a product must relate to the clinical situation unless clearly stated otherwise. The Panel noted that COPD was a chronic condition requiring long-term therapy. The reference given to support the claim, "[Serevent] has been shown ... to give COPD patients a significant improvement in lung-function and with a longer duration of action than ipratropium bromide", was a single dose study comparing Serevent and ipratropium in 12 patients with COPD. The Panel noted Boehringer Ingelheim's view, which appeared to be acknowledged by Glaxo Wellcome, that single dose studies had limitations in the extent to which results could be applied to chronic disease states. The Panel also noted that ipratropium required several weeks of dosing before a full response was achieved.

The Panel queried the relevance of the reference cited to the clinical situation. The Panel considered that many of the intended audience would assume that the claim and the referenced study related to long term therapy of COPD which was not so. The Panel considered that to use data from a single dose study, to support what would be assumed to be a clinical claim relating to chronic use, was misleading. A breach of Clause 7.2 of the Code was ruled.

The Panel noted that the part of the claim regarding the longer duration of action of Serevent compared to ipratropium was supported by clinical data. The data showed that Serevent maintained pretreatment morning FEV_1 at a higher level than ipratropium. The part of the claim relating to lung function, however, had not been substantiated and the Panel ruled a breach of Clause 7.3 of the Code.

3 Claim "Compared with ipratropium ... Serevent gives COPD patients a significantly greater improvement in mean morning peak flow ... ($p<0.001$)"

Boehringer Ingelheim stated that the claim appeared in a number of promotional pieces but the Panel could only find it in the detail aid in association with a graph which plotted changes in mean morning peak flow from baseline against time (12 weeks). The section was referenced to Bailey *et al* (1997).

COMPLAINT

Boehringer Ingelheim stated that in previous correspondence discussing the Bailey paper Glaxo Wellcome referred to "small differences in baseline morning peak expiratory flows". Boehringer Ingelheim quoted the results from the study which showed that salmeterol and ipratropium increased mean morning peak flow by 21.1L/min (8.46%) and 9.4L (3.44%) over baseline respectively; placebo decreased mean morning peak flow by 4.5L (1.7%).

Boehringer Ingelheim stated that these small changes in peak flow indicated a slight decrease in large airway resistance. Although statistically significant, these changes were clinically irrelevant. The symptomatic improvement observed in these patients was unlikely to be due to changes in the large airways, but to changes in the small airways and lung volumes. These were identified by measuring FEV_1 and forced vital capacity (FVC).

Boehringer Ingelheim summarised the changes observed in terms of FEV_1 and FVC. These results, Boehringer Ingelheim submitted, were more reliable measurements of changes in the small airways and were more significant than the changes observed through peak flow measurements. As opposed to the mere 8% and 3% changes observed with peak flows, FEV_1 increase from screening values was 36% in both the salmeterol and the ipratropium group on day one. Boehringer Ingelheim noted that the response to ipratropium was known to improve with time but that the actual values over consecutive visits were not given.

Boehringer Ingelheim stated that in terms of FEV_1 increase from baseline, the mean response with ipratropium (31%) was actually superior to that observed with salmeterol (21%). This might be due to a fault in the trial design, since the wash-out period of 12 hours did not take into account the difference in duration of action between both drugs. As a result of this, pretreatment values in the salmeterol group would have been artificially high. It was worth noting, however, that in terms of day time symptoms such as shortness of breath, cough and chest tightness the patients on ipratropium appeared to be better controlled.

Boehringer Ingelheim alleged that the claim, "Serevent gives COPD patients a significantly greater improvement in mean morning peak flow compared to ipratropium bromide ($p<0.001$)" and the accompanying graph did not represent a balanced view of the totality of the clinical data, were misleading and were thus in breach of Clause 7.2 of the Code.

RESPONSE

Glaxo Wellcome said that the claim in question, "Serevent gives COPD patients a significantly greater improvement in mean morning peak flow compared to ipratropium bromide ($p<0.001$)" was factually correct. Since its earlier correspondence with Boehringer Ingelheim it had become apparent that the baseline peak expiratory flow (PEF) data on Bailey's poster were in the incorrect columns but this had been corrected (data on file). Although the baseline mean morning PEF value for patients on ipratropium was significantly less than that of the placebo group, there was no real effect on the results of the analysis or the claim.

During the course of the study home recorded PEF increased slightly but statistically significantly ($p<0.001$) in patients taking ipratropium compared with placebo, while the mean morning PEF of patients on Serevent increased compared with those taking placebo and those taking ipratropium (data on file).

Glaxo Wellcome stated that, as explained in correspondence with Boehringer Ingelheim, the changes in mean morning PEF were chosen as most general practitioners were familiar with PEF measurement. Changes in FEV_1 itself did not always correlate with symptomatic improvement. Glaxo Wellcome noted that the European Respiratory Society's Consensus Statement (1995) "Optimal assessment and management of chronic obstructive pulmonary disease (COPD)" stated that "peak expiratory flow (PEF) is more convenient for domicilary monitoring of airway function. This measurement is sometimes used to assess response to treatment or to document diurnal variation".

Glaxo Wellcome stated that the peak flow measurements did reflect the changes in FEV_1 and symptoms. For all patients in the study, the pretreatment mean morning FEV_1 at weeks 4, 8 and 12 was significantly increased compared with pretreatment baseline levels and also compared with values in patients on ipratropium (data on file). From the patient's viewpoint the maintenance of a consistent level of lung function was desirable and that this occurred in the patients taking Serevent was evident in the plots of FEV_1 against time on the study days, at the first dose of blinded therapy and on the test days at 4, 8 and 12 weeks. Glaxo Wellcome provided data on file which gave information for the whole study group (813 patients), without subgroup analysis. The significantly higher pretreatment values for patients taking Serevent was evident and this was associated with longer overnight maintenance of effect and a reduction in nocturnal symptoms compared with placebo. With a higher starting point the percentage change in FEV_1 with a study dose would be less for those patients on Serevent compared with those on ipratropium in whom the morning FEV_1 would have fallen to levels approaching the baseline FEV_1 on day one. It was only after 12 weeks of the study that a pretreatment morning FEV_1 was higher than baseline in the ipratropium group and then it was only by 0.04 litres compared with 0.13 litres in the Serevent group (data on file). Glaxo Wellcome provided FEV_1 values and changes on study days, both graphically and in tabular form.

Glaxo Wellcome stated that in relation to daytime symptoms, the statement in the complaint that "patients on ipratropium appeared to be better controlled" was not supported by the p-values shown on the poster in terms of comparisons between the two active treatment groups.

Glaxo Wellcome considered that the claim "Serevent gives COPD patients a significantly greater improvement in mean morning peak flow compared to ipratropium bromide ($p<0.001$)" was factually correct, was supported by data which showed that the FEV_1 was better maintained in patients on Serevent compared with those on ipratropium. It was not misleading nor in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel considered it unfortunate that there had been errors in the poster by Bailey upon which Boehringer Ingelheim had based its complaint. The Panel noted that it had not seen the poster but according to Glaxo Wellcome figures had been placed in the wrong columns.

The Panel examined the data on file supplied by Glaxo and considered that it supported the claim "Serevent gives COPD patients a significantly greater improvement in mean morning peak flow compared to ipratropium bromide ($p<0.001$)". The claim clearly stated which parameter had been measured. In addition, significant differences between Serevent and ipratropium had been seen over the 12 week study period.

The Panel noted that the "data on file" submitted in support of the claim gave details only of 12 hour serial pulmonary function (FEV_1) and mean morning PEF measurements. The data on file gave results obtained from 813 patients and although no details of the investigators were given the data was assumed to be a part of the study referred to by Glaxo in its response to point 1. The Panel noted Glaxo Wellcome's submission in point 1 that "In this study, changes in most outcome variables were comparable but some were significantly in favour of salmeterol, such as nocturnal breathlessness, mean morning peak expiratory flow and the premedication morning FEV_1 ..". Glaxo Wellcome had submitted that this study showed that salmeterol was likely to be at least as effective as ipratropium in the treatment of COPD.

The Panel considered that the claim was factually accurate and supported by the data provided. The claim highlighted a measurement which the Panel considered the intended audience was likely to understand and be able to relate to clinical practice. The Panel noted the submission from Glaxo Wellcome regarding the European Respiratory Society's Consensus Statement which stated that PEF was more convenient for domicilary monitoring of airway function and that PEF was sometimes used to assess response to treatment or to document diurnal variation. The Panel considered that much was being made of one result from the study when overall the study results had been more equitable. On balance however the Panel did not consider that the claim was misleading and ruled no breach of Clause 7.2 of the Code.

Complaint received **28 October 1997**

Case completed **25 February 1998**

CASE AUTH/637/11/97

CONSULTANT PSYCHIATRIST v LOREX SYNTHÉLABO

Meeting in Cannes

A consultant psychiatrist complained about a symposium to be held in Cannes by Lorex Synthélabo . The invitation stated that it was a scientific meeting held over three days to discuss current issues in the management of schizophrenia and to review the new antipsychotic Solian (amisulpride). In the complainant's view, the level of hospitality was excessive, in particular the decision to locate the symposium in Cannes and the inclusion of sightseeing tours and a gala dinner. If the manufacturers were seriously interested in promoting a valuable product, whilst at the same time keeping the costs of that product down, a series of day meetings in various locations in the UK would be adequate.

The Panel noted that the Code did not prevent companies from holding meetings for UK health professionals at venues outside the UK. The impression created by the arrangements for a meeting had to be kept in mind. In the Panel's view the programme should attract delegates and not the venue. The Panel queried why the meeting had been held in Cannes given that the delegates and speakers were from the UK. It did not accept the submission that since Lorex Synthélabo was a French company it was appropriate to hold the meeting in France. The meeting could have been held in the UK. Although the educational content of the meeting was not unreasonable, with almost eight hours of presentations, it could have been held over a shorter time period. The afternoon excursions were inappropriate. The Panel considered that the cost of the meeting exceeded the level which those attending would normally adopt when paying for themselves. The arrangements for the meeting were unacceptable and a breach of the Code was ruled. The Panel considered that the educational content was not unreasonable and no breach of the Code was ruled in that regard.

Upon appeal by Lorex Synthélabo, the Appeal Board noted that all the circumstances had to be considered including cost, location, educational content, the level of associated hospitality and the overall impression created by the arrangements. The Appeal Board considered that while it was acceptable for companies to hold meetings at pleasant venues, it should be the programme that attracted delegates and not the venue. In the Appeal Board's view it was difficult for companies to justify holding meetings for UK health professionals at venues outside the UK. Attendance at an international scientific congress would be one exception to this.

The Appeal Board was critical of the use of the term "gala dinner". In the Appeal Board's view Cannes would be regarded as a luxurious location and it was highly likely that delegates would be attracted to the three day conference more by the venue and social programme than the relatively short educational programme. The cost was more than delegates might adopt if paying for themselves. The fact that Lorex Synthélabo was a French company was insufficient to justify holding the meeting in France. The Appeal Board considered that overall the arrangements were unacceptable and upheld the Panel's ruling that the Code had been breached.

A consultant psychiatrist complained about an invitation to a symposium from Lorex Synthélabo Ltd. The symposium was to be held from Wednesday 12 November to Friday 14 November 1997 at the Carlton International Hotel, Cannes, France, to mark the launch of Solian (amisulpride). The invitation stated that it was a scientific meeting to discuss current issues in the management of schizophrenia and to review the new antipsychotic Solian.

COMPLAINT

The complainant invited the Authority to consider whether this promotion fell outside the requirements of Clause 19 of the Code. In his view the level of hospitality was excessive, in particular the decision to locate the symposium in Cannes and the inclusion of sightseeing tours and a gala dinner.

The complainant stated that if the manufacturers were seriously interested in promoting a valuable product, whilst at the same time keeping the costs of that product down, a series of day meetings in various locations in the UK would be more than adequate.

RESPONSE

Lorex Synthélabo submitted that it was perfectly acceptable in principle for a pharmaceutical company to sponsor launch meetings, at home or abroad, for new products. For such meetings, the criteria of compliance with the Code were that they must have a predominant educational content, and that any hospitality provided must be secondary to the primary purpose of the meeting. Furthermore, such hospitality as was provided must be appropriate and not exceed a level which recipients would normally adopt when paying for themselves.

Lorex Synthélabo pointed out that at the Solian launch symposium, the educational sessions occupied three out of the four half-day sessions which comprised the meeting - a total of over seven and a half hours of scientific content. A copy of the delegate folder was provided. The first session was a state-of-the-art session on the management of schizophrenia, the second session reviewed the current scientific data on Solian in depth, and the third session was a general interest session of assorted scientific topics relevant to schizophrenia and the practice of psychiatry. The speakers were highly respected members of their profession, including two professors of psychiatry. The company therefore believed, that the scientific content of the meeting was exemplary in both quality and quantity.

Lorex Synthélabo submitted that since it was a French company it was appropriate to locate the meeting in France. This had the added benefit of involving similar costs to a comparable event organised in the UK in November, while allowing its French colleagues easy access to the meeting. Travel to the meeting involved a charter flight at a cost which compared favourably with internal UK flight costs and significantly less than an economy air fare to the conference venue. Lorex Synthélabo submitted that entertainment of the delegates

was at all times appropriate and involved only dinner on two evenings and the option of a coach trip to one of three nearby places of interest in the one period of free time. There were no other activities listed in the programme.

Lorex Synthélabo provided details of the main budgeted delegate costs for the meeting. The budgeted cost per head was £598. Lorex Synthélabo stated that it had no reason to suppose that final costs, when they had been collated, would be significantly different. The final attendance was 143 delegates plus 10 speakers, together with 20 staff from Synthélabo and Fusion. A list of invitees was provided.

In summary, Lorex Synthélabo stated that the cost of organising such an event in the UK or Cannes was not significantly different. The programme was predominantly scientific and, as required by the Code, any entertainment was modest and at a cost that the participants would expect to pay themselves. The particular areas drawn attention to by the complainant, namely the gala dinner and coach trips, were both, in its view, entirely appropriate for an event of this kind.

Lorex Synthélabo submitted that it had behaved entirely properly in the organisation of this symposium and had provided a meeting of high educational quality and quantity at a cost comparable to that which would be involved in the UK.

PANEL RULING

The Panel noted that Clause 19 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 delegates, who were mainly consultant psychiatrists, would fly to Cannes on a chartered flight from London Gatwick on Wednesday 14 November. The educational part of the meeting commenced that afternoon at 2.30 until 5.00pm. This was followed by dinner in small groups in local restaurants to sample local provençale cuisine. The second session on Thursday ran from 9.15am until 12.30 including a 35 minute coffee break. This was followed by an afternoon of leisure. Lorex Synthélabo provided an excursion to a nearby place of interest (Monaco, Nice or Saint Paul de Vence) followed by a gala dinner. The third and final educational session commenced at 9.00 on the Friday morning and finished at 11.20am. The charter flight from Nice to Gatwick left that afternoon. The Panel considered that although the actual educational content of the meeting was not unreasonable, there were almost eight hours of presentations, it could have been held over a shorter time period.

The Panel queried why the meeting had been held in Cannes given that the delegates and speakers were from the UK. The Panel did not accept the submission that since Lorex Synthélabo was a French company it was appropriate to hold the meeting in France. The Panel noted that some of the head office staff had attended the meeting but the primary purpose of the meeting was to mark the launch of Solian in the UK. The meeting could have been held at a location in the UK. The Panel noted that the budgeted cost of the meeting had been estimated at £598 per head. The Panel considered that the impression given by using the term "gala dinner" was most unfortunate although the budgeted cost of £55 per head was not unreasonable. The Panel considered that the excursion paid for by the company at a budgeted cost of £25 per head was inappropriate. It might be possible to justify the inclusion of a low key appropriate excursion when meetings were of a longer duration than the one in question.

The Panel considered that the budgeted cost of the meeting at £598 exceeded the level that those attending 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 considered that as the educational content was not unreasonable there was no breach of Clauses 2 or 9.1 of the Code and ruled accordingly.

APPEAL BY LOREX SYNTHÉLABO

In appealing the Panel ruling, Lorex Synthélabo asked that the Appeal Board first consider two questions:

1 Was it acceptable under certain circumstances for UK based pharmaceutical companies to host meetings for UK doctors outside the UK?

2 Was it not acceptable under any circumstances for UK based pharmaceutical companies to host meetings for UK doctors outside the UK?

If the Appeal Board considered that the latter was the case, then Lorex Synthélabo asked that the Appeal Board rule accordingly so that companies could be in no doubt as to how the Code was to be interpreted.

If the former was the case, which was Lorex Synthélabo's understanding of the situation, the problem of interpretation that arose occurred in the supplementary information to Clause 19. This stated that the impression that was created by the arrangements for any meeting must always be kept in mind. This could be seen as being tantamount to saying that regardless of the fact that a meeting had an exemplary educational content and regardless of the fact that a company had arranged the meeting inexpensively, well within the level that the participants would adopt when paying for themselves, the fact that the meeting was held at a venue abroad which might give an impression of being lavish and/or expensive was sufficient on its own to breach the Code.

An impression was by its very definition, highly subjective. What was an attractive venue to one person might not be viewed in the same way by another. Lorex Synthélabo maintained that the scientific programme for the meeting was highly attractive in itself to an audience

of consultant psychiatrists, consisting as it did of a number of presentations discussing the current state-of-the-art in the management of schizophrenia, many of the presentations being given by psychiatrists of international standing. In addition, the programme contained new data on the innovative anti-schizophrenia drug amisulpride which would be of great interest to an audience of psychiatrists because of the potential it had in improving patient treatment in schizophrenia. Lorex Synthélabo therefore believed that the programme itself was sufficiently attractive for consultant psychiatrists to want to attend the meeting, almost irrespective of the venue.

Having said that, Lorex Synthélabo made the point that this was no ordinary meeting. It was the most important meeting that a company arranged for a product during its life - its launch. This was by definition a one-off affair and the company would submit that in recognition of the uniqueness and importance of a product launch, a slightly higher standard of hospitality and possibly a more attractive venue was more likely to be acceptable for a launch meeting than for a routine educational/promotional meeting held later on in a product's life cycle.

The Panel, in its ruling, made certain further points regarding the arrangements for the meeting:

1 The meeting could have been held over a shorter time period.

2 The meeting could have been held in the UK.

3 The term "gala dinner" was most unfortunate.

4 An afternoon free with optional excursions was excessive in a meeting lasting two days.

5 The budgeted cost of the meeting at £598 per head exceeded the level that recipients would adopt when paying for themselves.

Taking each of these points in turn:

1 Lorex Synthélabo did not accept that the meeting as it was (ie, in a venue in France) could have been held in a time that was significantly shorter. It could have started the meeting on the Wednesday afternoon and run the Friday morning session on the Thursday afternoon rather than giving the delegates time off, but the net effect would have been the same in that the participants would make their way home on the Friday anyway, and unless they took particularly early flights they would probably arrive home at about the same time.

2 Of course the meeting could have been held in the UK, but Lorex Synthélabo was a French company which was part of a large French based multinational group (L'Oreal) and as a result it could negotiate very competitive conference rates in France, more so than it could in the UK.

Preliminary enquiries at the time of planning the conference revealed that the costs would be about the same to hold the meeting in Cannes as they would be for a decent venue in the UK. Lorex Synthélabo provided quotations obtained for holding the meeting at a UK venue. For the meeting the Belfry Hotel in Warwickshire would have charged £98,580, The Royal Garden Hotel in London £113,030, whereas the quoted cost for the Carlton Hotel in Cannes including charter flights was £111,540. In fact the actual cost worked out in the end to be slightly less at a total of £104,570 for the principal costs.

Lorex Synthélabo also believed that its expenditure on travel for this meeting was very economical as the cost per head for the chartered aircraft was £258, which compared very favourably with the standard midweek economy return to Nice of £462 (BM) or £472 (BA). In particular, this cost (£258) also compared well with the cost of internal flights in the UK and 1st class rail fares if the meeting was held in the UK.

3 Lorex Synthélabo agreed that the impression given by the term "gala dinner" was unfortunate, but the term seemed to have been inappropriately carried over from internal sales conferences. Lorex Synthélabo undertook not to use this term in future with reference to any hospitality provided to healthcare professionals.

4 Considering that the delegates had to spend time travelling to and from the conference, and that the conference itself consisted of almost eight hours of presentations and interactive discussion sessions, Lorex Synthélabo submitted that an afternoon free with optional coach tours (each lasting about four hours including stopover) was not unreasonable. These tours were not compulsory, and delegates were free to spend the time in other ways, such as continuing discussions with speakers and other delegates on scientific matters regarding schizophrenia and/or the product amisulpride, or just matters of general interest to practising psychiatrists.

5 The Panel considered that the cost of the meeting (£598) exceeded the level that the recipients (ie, psychiatrists of consultant grade) would adopt when paying for themselves.

Clearly this was purely a matter of opinion on the part of the Panel with which Lorex Synthélabo could not agree.

Lorex Synthélabo believed that doctors of consultant status were professional people of high standing who enjoyed a good level of remuneration. Such people would, it believed, happily pay £598 for a three day trip to Europe with two nights in a hotel with meals included. Referring to point 2 above, Lorex Synthélabo drew the attention to the fact that the lowest price for an economy midweek return air ticket alone to Nice was £462.

In summary, Lorex Synthélabo believed that the Code allowed meetings for UK physicians to be held outside the UK as long as the educational content predominated and that the hospitality offered was secondary to the main purpose of the meeting and was not excessive. Indeed the General Medical Council guidance in its publication 'Good Medical Practice' stated that the amount of travel grants or hospitality "must not be more than you would normally spend if you were paying for yourself".

In this case, Lorex Synthélabo believed that consultant psychiatrists would have no doubts that the main purpose of this event was educational and that the level of hospitality offered was consistent with their professional standing.

Lorex Synthélabo also believed that the launch of a new medicine was a unique occasion for a company and its product and, as such, the impression of a slightly higher level of hospitality would be appropriate where it might not be for a meeting involving a product that had been on

the market for several years.

APPEAL BOARD RULING

The Appeal Board noted that when considering whether a meeting and associated hospitality contravened Clause 19.1 of the Code all the circumstances had to be considered including cost, location, educational content, the level of associated hospitality and the overall impression created by such arrangements. Each case had to be considered on its own merits.

The Appeal Board noted that the Code did not prevent companies from holding meetings for UK health professionals at venues outside the UK but considered that there had to be valid and cogent reasons for so doing. The impression created by the arrangements for any meeting must be kept in mind. The Appeal Board considered that while it was acceptable for companies to hold meetings at pleasant venues, it should be the programme that attracted delegates and not the venue. In the Appeal Board's view it was difficult for companies to justify holding meetings for UK health professionals at venues outside the UK. Attendance at an international scientific congress would be one exception to this.

The Appeal Board noted that the educational content of 7½ hours was spread over 3 days. The invitation to the meeting included details of the presentations and also gave details of the social programme. At the same time as booking delegates were asked to choose which afternoon excursion they would wish to go on. The Appeal Board was critical of the use of the term "gala dinner". In the Appeal Board's view Cannes would be regarded as a luxurious location and it was highly likely that delegates would be attracted to the three day conference more by the venue and social programme than the relatively short educational programme. The Appeal Board considered that the cost of the meeting, at £598 per head, exceeded the level that delegates might adopt if paying for themselves. The Appeal Board noted that Lorex Synthélabo was a French company but considered that this, in itself, was insufficient to justify holding the meeting in France.

The Appeal Board considered that overall the arrangements for the meeting were unacceptable and upheld the Panel's ruling of a breach of Clause 19.1 of the Code.

The respondent's appeal therefore failed.

Complaint received **3 November 1997**

Case completed **19 March 1998**

CASE AUTH/639/11/97

SMITHKLINE BEECHAM v BAYER

Ciproxin clinical reference file and guide

SmithKline Beecham complained about a table appearing in a Ciproxin reference guide and a clinical reference file. The table was labelled "Antibiotics associated with *C.difficile* - induced colitis" and listed antibiotics under three headings, "frequent", "infrequent" and "rare". SmithKline Beecham's co-amoxiclav (Augmentin), a fixed combination of amoxycillin and clavulanic acid, was included in the column headed "frequent". SmithKline Beecham complained that it could find no reference in the article from which the table had been taken to identify the source of the data used to compile the table. The paragraph in the article which referred to the table specifically mentioned clindamycin, ampicillin/amoxycillin and the cephalosporins, all of which were referenced to evidence based studies. No such study was referred to for co-amoxiclav yet it was included in the table under the heading "frequent". SmithKline Beecham alleged that the claim was misleading and not substantiated.

The Panel noted that the only requirement in the Code relating to the need to give references was when the promotional material referred to published studies. If a reference was given it need not be such as to fully substantiate the information to which it applied though clearly it had to be relevant and supportive. All promotional material had to be capable of substantiation but not all promotional material needed to be referenced. Having reviewed the available evidence, the Panel considered that the promotional material did not preclude the possibility that some or all of the antibiotics which appeared in the "frequent" column were those which were the most widely prescribed. It appeared that no account had been taken of the widespread use of such products. The Panel considered that the material was misleading and ruled it in breach.

SmithKline Beecham Pharmaceuticals UK submitted a complaint about two pieces of promotional material produced by Bayer Plc Pharmaceutical Division for its product Ciproxin (ciprofloxacin). A Ciproxin reference guide (ref 9BCPT874) and a clinical reference file (ref 9BCPT818), in sections respectively headed "Cut the risk down to size with Ciproxin" and "An overview of the incidence and consequences of *C.difficile*-induced colitis", both contained a table extracted in its entirety from an article by Buckley (1996). The table was labelled "Antibiotics associated with *C.difficile*-induced colitis". The table listed antibiotics under three headings, "frequent", "infrequent" and "rare". SmithKline Beecham's product co-amoxiclav (Augmentin), a fixed combination of amoxycillin and clavulanic acid, was included in the column headed "frequent".

COMPLAINT

SmithKline Beecham complained that it could find no reference in the Buckley (1996) article to identify the source of data used to compile the table in question. SmithKline Beecham stated that the paragraph in the article which referred to the table specifically mentioned the antibiotics implicated as clindamycin, ampicillin/amoxycillin and the cephalosporins, all of which were referenced to evidence based studies. No such study was referred to for co-amoxiclav yet it was included in the table as "frequently" associated with *C.difficile*-induced colitis (CDIC).

SmithKline Beecham pointed out that prior to the submission of this complaint it had asked Bayer to comment on the Buckley article and its use in the clinical reference file and guide. In response Bayer had cited references which it believed supported the use of the claim made by Buckley (Kelly *et al* (1994); Rao *et al* (1997); Reinke and Messick (1994); Vautrin *et al* (1993)). SmithKline Beecham was of the opinion that these references did not support the use of the claim and, furthermore, they were not cited in the promotional material as substantiating data.

SmithKline Beecham stated that the articles by Kelly *et al* (1994) and Reinke and Messick (1994) were reviews and made no reference to co-amoxiclav. The articles by Rao *et al* (1997) and Vautrin *et al* (1993) did not support the claims made by Bayer. SmithKline Beecham provided the Panel with a copy of its letter to Bayer in which it expressed its concerns about these articles in detail and Bayer's letter of response which SmithKline Beecham submitted did not substantiate its claim that co-amoxiclav was frequently associated with CDIC.

SmithKline Beecham alleged that the claim was misleading and not substantiated and therefore was in breach of Clauses 7.2 and 7.3 of the Code.

RESPONSE

Bayer pointed out that the clinical reference file was no longer in current use. Bayer stated that the article by Buckley (1996), which SmithKline Beecham considered to offer unsubstantiated claims related to the frequency of *C.difficile*-induced colitis (CDIC) in patients receiving co-amoxiclav, was considered by Bayer to represent current opinion and to be substantiated by a wide body of evidence in the literature.

Bayer did not therefore accept SmithKline Beecham's allegations of a breach of Clauses 7.2 and 7.3 of the Code. Bayer believed that the claims in question were neither misleading nor unsubstantiated.

Bayer referred to the table in the article "The treatment of CDIC" by Buckley published in Pharmacy in Practice, February 1996. Bayer noted that the complaint appeared to be based upon the inclusion of co-amoxiclav in the category as "frequently" associated with CDIC, along with agents such as cephalosporins and amoxycillin, without a specific evidence-based reference being quoted in the review. Bayer submitted that there was a wide body of evidence available in the current scientific literature to support the Buckley review.

Bayer stated that Vautrin (1993) found that co-amoxiclav was the most common antibiotic treatment responsible for *C.difficile* infections in a 12 month study. In addition, Rao

(1997) presented data from a retrospective study and found that "treatment with antibiotics, especially cephalosporins or co-amoxyclav [sic] are significant risk factors associated with the infection".

The Merck manual (1992) cited penicillins (and hence co-amoxiclav) as one of the groups of antibiotics most frequently implicated in pseudomembranous colitis.

Bayer pointed out that prior to the submission of the complaint SmithKline Beecham had already admitted in correspondence with Bayer "... that broad spectrum antibiotics which disrupt the normal colonic microflora are more commonly associated with *C.difficile*-induced colitis (CDIC) is generally accepted". Bayer stated that this admission was based upon the views expressed by Kelly (1994) and Reinke and Messick (1994).

Bayer stated that Kelly (1994) reported that "...*C.difficile* infection is responsible for virtually all cases of pseudomembranous colitis..." and regarding *C.difficile* infection, that "In current practice, however, broad-spectrum penicillins and cephalosporins are the most common culprits...". The paper listed amoxycillin (and hence potentiated amoxycillin) as a frequent inducer of CDIC.

Bayer submitted that SmithKline Beecham had specifically promoted the broad spectrum of activity of co-amoxiclav, highlighting its anaerobic cover and hence its usefulness in surgery. The Reinke and Messick review (1994) explained that "...antimicrobials that have the most deleterious effect on resistance to colonization are also among those most commonly associated with CDIC".

Bayer referred the Panel to a previous case, Case AUTH/479/12/96 regarding the promotion of Ciproxin. The Appeal Board had accepted that there was data to show that co-amoxiclav was more likely to be associated with the risk of pseudomembranous colitis than Ciproxin.

PANEL RULING

The Panel noted that Case AUTH/479/12/96 concerned a claim "Not only does Ciproxin demonstrate significantly fewer gastro-intestinal side effects than co-amoxiclav ... but the risk of pseudomembranous colitis is minimised with Ciproxin - less than 0.01% in a worldwide study of 9,466 patients". The Appeal Board had accepted that the data substantiated the claim. The Panel noted that in Case AUTH/479/12/96 the risk of pseudomembranous colitis with co-amoxiclav had not been quantified.

Turning to the case now before it the Panel examined the article by Buckley (1996) entitled "The treatment of CDIC". The table in question was labelled "Antibiotics associated with CDIC" and the accompanying text discussed the causal link between CDIC and broad and narrow spectrum antibiotics. The Panel noted that the terms "frequent", "infrequent" and "rare" were not quantified in the Buckley article.

The Buckley article stated that "In current practice, the penicillins and cephalosporins are the biggest causative agents, reflecting their widespread use". Kelly (1994) reproduced a table headed "Antimicrobial Agents That Induce *C. Difficile* - Associated Diarrhoea and Colitis" which was similar to the table on the Buckley article. The antibiotics were classified under the following headings: frequent induction, infrequent induction, rare or no induction. These headings were not quantified in the accompanying text nor did co-amoxiclav appear in the table, but Kelly stated that "...broad-spectrum penicillins and cephalosporins are the most common culprits, reflecting their widespread use." Reinke and Messick (1994) noted the classification of antimicrobial agents into three groups with respect to their potential to precipitate CDIC by Bartlett and the classification adapted by Kelly *et al* (1994) but did not state whether those antimicrobial agents which were commonly associated with CDIC were commonly prescribed. Reinke and Messick (1994) stated that "Numerous studies have demonstrated that, in addition to clindamycin and ampicillin, the cephalosporins are associated with CDIC relatively frequently". The paper included a table headed "Antimicrobial and Antineoplastic Agents that Can Precipitate *Clostridium difficile*-induced Colitis (CDIC)". Ampicillin and amoxycillin appeared beneath the heading "most common". The other columns were headed "less common" and "least common".

Rao *et al* (1997) stated that treatment with antibiotics, especially cephalosporins or co-amoxiclav were significant risk factors associated with *C.difficile* infections. The abstract also stated that "...control of indiscriminate use of antibiotics such as cephalosporins and co-amoxyclav [sic] is the only realistic and achievable method of preventing and controlling these infections".

Vautrin *et al* (1993) referred to a survey after 22 cases of diarrhoea caused by *C.difficile* in a geriatric hospital. The Panel noted that it appeared that amoxycillin and clavulanic acid treatment was the most frequently responsible antibiotic (65%).

The Panel noted that the only requirement in the Code relating to the need to give references was when promotional material referred to published studies. If promotional material gave a reference then that reference need not be such as to fully substantiate the information to which it applied though clearly it had to be relevant and supportive. All promotional material had to be capable of substantiation but not all promotional material needed to be referenced.

The Panel noted that both pieces of promotional material included details about the incidence of pseudomembranous colitis with Ciproxin as 0.01% in a review of studies of 9,466 patients worldwide. The Ciproxin reference guide described this as "very rare" whereas the clinical reference file described it as "rare".

The Panel considered that the promotional material did not preclude the possibility that some or all of those antibiotics, including co-amoxiclav, which appeared in the "frequent" column were those antibiotics which were the most widely prescribed. It appeared that no account had been taken of the widespread use of such products. The Panel considered therefore that the promotional material was misleading and ruled a breach of Clause 7.2 of the Code.

The Panel considered that in view of its ruling of a breach of Clause 7.2, there was no need to consider the allegation of a breach of Clause 7.3 of the Code.

Complaint received **7 November 1998**

Case completed **20 February 1998**

CASE AUTH/643/11/97

NO BREACH OF THE CODE

DOCTOR v GLAXO WELLCOME

Substantiation of claim

A doctor said that he had requested from Glaxo Wellcome the data on file referenced in a Zantac advertisement in relation to the claim "- how so many millions of patients in over 100 countries have been helped by Zantac". The complainant said that the company cited sales data and estimates of the number of prescriptions to support the claim implying that if the medicine had been prescribed, the patients must have been helped. The complainant alleged that this was of course untrue and the claim could not be accepted as having been substantiated.

The Panel noted that it was an accepted principle of the Code that data referenced in an advertisement need not be such as to fully substantiate the claim to which it was applied though clearly it had to be relevant to, and supportive of, that claim. It appeared to the Panel that the complainant had asked for the data referenced and that request had been met. The complainant had not asked for the claim to be substantiated. The Panel reviewed data submitted to it by Glaxo Wellcome, efficacy studies and the sales data, and considered that it was sufficient to substantiate the claim. No breach of the Code was ruled.

A doctor submitted a complaint about a claim in an advertisement for Zantac (ranitidine) which appeared in Prescriber on 5 December 1996. The claim in question appeared beneath the product name "Zantac" and stated "- how so many millions of patients in over 100 countries[1] have been helped by Zantac". Reference 1 was given as data on file.

COMPLAINT

The complainant had written to Glaxo Wellcome requesting the data on file referred to in the advertisement. A copy of the company's response was provided. The complainant pointed out that the company cited sales data and estimates of the number of prescriptions to support the claim that many millions of patients had been helped by Zantac, implying that, if the medicine had been prescribed, the patients must have been helped. The complainant alleged that this of course was untrue and the claim could not be accepted as having been substantiated. He alleged a breach of Clauses 7.3 or 7.4 of the Code.

RESPONSE

Glaxo Wellcome provided a list of countries where Zantac was now registered which totalled 110. The company also provided figures derived from estimates provided by Intercontinental Medical Statistics (IMS) representing the numbers of prescriptions written around the world for Zantac between 1981 and 1994, totalling 558,985,000.

Glaxo Wellcome stated that Clause 7.4 of the Code required that companies substantiated any information, claim or comparison without delay, at the request of members of the health professions or appropriate administrative staff. The advertisement for Zantac (In jean ious) made a claim that Zantac had helped many millions of patients in over 100 countries. Glaxo Wellcome submitted that the references substantiated that over 100 countries now had Zantac available and nearly 560 million patients had received it.

Glaxo Wellcome pointed out that it did not of course suggest that every single patient who had received Zantac had received benefit or even been helped by it. Glaxo Wellcome suggested that in fact the claim was quite modest, suggesting that of nearly 560 million prescriptions written only many millions would have helped their recipients. This was quite in line with the known efficacy of Zantac which would have been the basis of licence applications in each country.

Glaxo Wellcome referred to Grant *et al* (1989), an independent and comprehensive review of ranitidine and Mills *et al* (1997), a more recent evaluation of the safety of ranitidine in over a decade of use. Mills *et al* (1997) referred to 209 million patient treatments and both papers confirmed the good safety record and undoubted efficacy of ranitidine.

Glaxo Wellcome pointed out that a useful meta-analysis of duodenal ulcer healing trials by McIsaac *et al* (1987) looked at 31 comparative trials and confirmed healing rates on ranitidine of between 62 and 95% over 4 weeks. Ulcer healing after 2 and 4 weeks on various ranitidine dosages was again reviewed in 1991 giving rates of 40.5 to 68.2% at 2 weeks, and 67.6 to 95.5% at 4 weeks. Ireland *et al* in 1984 reported that ranitidine could produce duodenal ulcer healing rates of 96% at 4 weeks. This was undeniably helpful. Butruk *et al* had produced similar results - 94% healing at 4 weeks.

Glaxo Wellcome stated that over the years it had invested significant resources in monitoring Zantac in clinical trials looking at its efficacy and tolerability, employing up to 15 full-time personnel. This was the largest single team within Clinical Research in the company and was testimony to the commitment Glaxo Wellcome gave to supporting the development of this highly successful medicine (both in clinical efficacy and sales terms).

Glaxo Wellcome questioned whether the complainant was suggesting that doctors would have continued to prescribe Zantac over the last 13 years if it was not benefiting many, if not the majority, of its recipients?

Glaxo Wellcome submitted that the claim that millions of patients had been helped by Zantac could be assumed with confidence. Therefore it did not consider that a breach of Clause 7.4 had occurred.

It thought that both the provision of the substantiation, and indeed the substantiation itself, had been forthcoming and therefore there had been no breach of either Clause 7.3 or 7.4.

PANEL RULING

The Panel noted that Clause 7.3 of the Code stated that any information, claim or comparison must be capable of

substantiation and that Clause 7.4 stated that such substantiation must be provided on request without delay, but that it need not be provided in relation to the validity of indications approved in the marketing authorization.

The Panel noted that Zantac tablets, syrup and injections were indicated for the treatment of, *inter alia*, duodenal ulcer, benign gastric ulcer, postoperative ulcer, oesophageal reflux disease, Zollinger-Ellison syndrome and the prophylaxis of gastrointestinal haemorrhage from stress ulcer.

The Panel considered the comparative efficacy data submitted by Glaxo Wellcome. Firstly the Panel considered the paper by Grant *et al* (1989) entitled Ranitidine - An Updated Review of its Pharmacodynamic and Pharmacokinetic Properties and Therapeutic Use in Peptic Ulcer Disease and Other Allied Diseases, which concluded that overall ranitidine was comparable or superior to most peptic ulcer treatments in the management of conditions exacerbated by gastric acid secretion, and had a well established high degree of efficacy in treating and preventing gastrointestinal lesions aggravated by gastric acid secretion. The paper by McIsaac *et al* (1987) examined the data from trials comparing the effects of cimetidine and ranitidine on the rate of duodenal ulcer healing and subjected these to a meta-analysis in an attempt to assess the differences between the two products for some of the various H_2-receptor antagonist dosage regimens. The study concluded that it was clear from the evaluation of all available studies that both ranitidine and cimetidine healed ulcers rapidly but that ranitidine 150mg twice daily healed significantly more ulcers after 4 weeks of therapy than either 1g daily or 400mg twice daily of cimetidine.

The Panel noted that Zantac was marketed in 105 countries world-wide and had approved registration status in a further 5 countries. The Panel noted that in 9 key countries the total number of prescriptions written between 1981 and 1994 was 432,646,000. This total comprised actual and estimated data. The estimated worldwide number of prescriptions written between 1981 and 1994 was 558,985,000.

The Panel noted that it had received from the complainant a letter dated 4 February 1997 sent to him by Glaxo Wellcome in response to his enquiry about the advertisement in question. The letter from Glaxo Wellcome referred to an enclosed list of countries where Zantac was sold and IMS sales data showing that between 1981 and 1994 over 500 million prescriptions had been written. Glaxo Wellcome stated in its letter that this data was provided "in support" of the claim "- how so many millions of patients in over 100 countries have been helped by Zantac". Glaxo Wellcome did not state that the enclosures substantiated the claim. None of the enclosures had been provided with the complaint.

The Panel noted that according to the sales data submitted by Glaxo Wellcome in its response to the Authority, the estimated number of prescriptions written for Zantac between 1981 and 1994 was 558,985,000 and that as Zantac was a licensed medicine it must have demonstrated efficacy in order to obtain its licences and hence a significant proportion of patients who had been prescribed Zantac would have been helped. The Panel did not accept that the claim "- how so many millions of patients in over 100 countries have been helped by Zantac" implied that all patients prescribed Zantac must have been helped.

The Panel considered that the material provided by Glaxo Wellcome to the Panel, the efficacy studies and the sales data, was sufficient to substantiate the claim "- how so many millions of patients in over 100 countries have been helped by Zantac".

The Panel noted that it had not seen the original letter sent by the complainant to Glaxo Wellcome. According to the complainant's letter to the Authority he had asked Glaxo Wellcome to send him the data on file referred to in the advertisement. This had been sent to him. It appeared to the Panel that the complainant had not asked for the claim to be substantiated. The Panel noted that it was an accepted principle of the Code that data cited in an advertisement need not be such as to fully substantiate the claim to which it was applied, though clearly it had to be relevant to, and supportive of, that claim. The Panel noted that the reference 1 appeared after "- how so many millions of patients in over 100 countries" and not at the end of the claim. The Panel was of the opinion that the complainant's request for the cited data on file had been met appropriately and ruled that Clauses 7.3 and 7.4 of the Code had not been breached.

Complaint received **13 November 1997**

Case completed **2 February 1998**

CASE AUTH/644/11/97

HOSPITAL PHARMACIST v PHARMACIA & UPJOHN

Information on growth hormone

A hospital pharmacist complained about material on growth hormone (GH) sent by Pharmacia & Upjohn. The material consisted of a plastic wallet labelled "GH Therapy Update" inside which was a four page A4 newsletter entitled "GH Therapy Update". The back page stated that it was published by Pharmacia & Upjohn and a reply paid card could be returned to the company for further information. The wallet was accompanied by a letter from the editor of the newsletter, a consultant endocrinologist, and this bore no reference to Pharmacia & Upjohn. The complainant alleged that the material appeared to be a promotional mailing for growth hormone under the guise of educational material.

The Panel noted that the newsletter gave detailed information about treatment and, in the Panel's view, encouraged the use of growth hormone to treat adult growth hormone deficiency. The Panel considered that it went further than the exemption given by the Code which stated that promotion did not include statements relating to human health or diseases provided that there was no reference, either direct or indirect, to specific medicines. No products were mentioned by name in the newsletter but reference was made to growth hormone therapy in adults and its benefits. The Panel considered that the nature of the material and Pharmacia & Upjohn's involvement meant that the mailing in effect amounted to promotion of Pharmacia & Upjohn's product, Genotropin. A breach was ruled as the mailing as a whole was considered to constitute disguised promotion.

Upon appeal by Pharmacia & Upjohn, the Appeal Board considered that the material promoted growth hormone as a class and there was more than one medicine within that class on the UK market. It did not refer to any specific medicine and was not promotion and could not therefore be in breach as disguised promotion. No breach was ruled.

The Panel also ruled that the newsletter was in breach because, though its sponsorship was declared, it was not made sufficiently clear to those reading it. The letter was in breach because no mention was made of the fact that Pharmacia & Upjohn had produced and distributed the material. These rulings were accepted by Pharmacia & Upjohn.

A hospital pharmacist submitted a complaint about material on growth hormone (GH) sent by Pharmacia & Upjohn Limited .

The material consisted of a plastic wallet labelled "GH Therapy Update". The reverse stated that it was "Provided as an educational service by Pharmacia & Upjohn". Inside the folder was a four page A4 newsletter entitled "GH Therapy Update" The newsletter was dated October 1997 and labelled Issue 1. It stated that the editor was a consultant endocrinologist. The newsletter discussed growth hormone replacement therapy in adults and referred to the incidence and prevalence of adult growth hormone deficiency, cost of therapy, treatment protocols and the effect of growth hormone on body composition and cardiovascular risk factors. The back page of the newsletter stated that GH Therapy Update was published by Pharmacia & Upjohn. A reply paid card was also enclosed in the folder with which recipients could request further information about growth hormone deficiency in adults and its treatment. The reply paid card was addressed to the Product Manager - Metabolic Care, Pharmacia & Upjohn.

The plastic wallet was accompanied by a letter from the consultant endocrinologist on notepaper headed with the name of the hospital and department within which the consultant was based. The letter introduced the quarterly newsletter and stated that it would provide a broad overview of the main issues relating to growth hormone deficiency in adults. The letter referred to the relative rarity of adult growth hormone deficiency and, coupled with the fact that treatment had only recently become established, stated that it was particularly important that accurate and timely information should be readily available. The covering letter made no reference to Pharmacia & Upjohn.

COMPLAINT

The complainant alleged that the material in question appeared to be a promotional mailing for growth hormone under the guise of "educational material" with a personal communication from a consultant endocrinologist. A breach of Clause 10.1 was alleged.

RESPONSE

Pharmacia & Upjohn denied any breach of the Code. The company explained that the prevalence, diagnosis and management (including the cost) of adult growth hormone deficiency were complex and currently poorly understood. There was a lack of awareness of the condition amongst many clinicians. As a result those managers in the NHS responsible for planning healthcare provision often found it difficult to obtain sufficient factual information to support their decisions. The GH Therapy Update newsletter was an attempt to provide useful data and information about the therapeutic area to aid such decision making.

GH Therapy Update Issue 1, its wallet, the reply paid card and the covering letter from the consultant endocrinologist were all produced and distributed by Pharmacia & Upjohn. The consultant was asked by the company to edit the series of newsletters. The material was sent personally to all 125 health authorities, health boards and health and social services boards. It was sent to chief executives, medical advisers, pharmaceutical advisers, directors of public health, consultants in public health and drug information pharmacists. It was not sent to any endocrinologists or GPs (with the exception of a courtesy copy to the editor). Thus the material was not sent to any person who was known to have direct prescribing responsibility for growth hormone.

Pharmacia & Upjohn said that in the UK there were five growth hormone manufacturers, Pharmacia & Upjohn, Novo Nordisk, Eli Lilly, Serono and Ferring. Growth

hormone products from Novo Nordisk, Eli Lilly and Pharmacia & Upjohn were currently licensed for and marketed for the adult growth hormone deficiency indication. The licences were received in 1996. The Pharmacia & Upjohn brand, Genotropin, was made available for pronounced growth hormone deficiency in adults in March 1996.

Pharmacia & Upjohn submitted that its involvement in the production and distribution of the material in question was not concealed. It was clearly stated on the final page where, in addition to the logo, the name of the company appeared four times. The reply paid card was addressed to Pharmacia & Upjohn and the back of the plastic wallet included the statement "Provided as an educational service by Pharmacia & Upjohn". The address of the company was also given.

The material was sent in a plain white envelope with a printed name and address label on the front and there was no other wording on the envelope implying that the contents were either promotional or non-promotional. Nowhere on the material was there any mention of Pharmacia & Upjohn's own brand of growth hormone. The company submitted it was not promoting its medicine and in this context referred to Clause 1.2 of the Code.

Pharmacia & Upjohn summarised that the material was provided to NHS decision makers. It contained current, independently reviewed clinical and cost related data. There was no mention of Pharmacia & Upjohn's own brand of growth hormone. Its involvement in the material was not concealed. It did not accept that the material contravened Clause 10.1 of the Code.

PANEL RULING

The Panel examined the newsletter which referred to the effects of untreated growth hormone deficiency in adults and the evidence for recommending treatment. The newsletter stated that only around 50% of patients would have a severe enough deficiency and would respond to therapy. The benefits of growth hormone replacement therapy were also given in the newsletter.

The Panel noted Pharmacia & Upjohn's submission that the material was exempt from the Code as it was not promoting its medicine. The Panel noted that Clause 1.2 of the Code stated that the term promotion did not include "Statements relating to human health or diseases provided there was no reference, either direct or indirect, to specific medicines".

The Panel noted two other cases which raised similar issues to the case now before it. The first, Case AUTH/296/5/95, concerned a booklet on peptic ulcer disease sent to NHS managers. The Panel had considered that the material in question, although not product specific, was subject to the Code as it was company produced material on a disease area in which the company was commercially interested. The booklet focused on peptic ulcer disease and referred to appropriate maintenance therapy to decrease the costs associated with peptic ulcer disease by reducing the need for repeated investigations, consultation and hospital admission. The booklet was ruled in breach of Clause 7.2 of the Code as it was not up to date due to the lack of acknowledgement of the role of *Helicobacter pylori* eradication. This ruling had been upheld by the Appeal Board.

The Panel also referred to Case AUTH/516/3/97 which concerned a disease area campaign to the public. Clause 20.2 of the Code required that statements must not be made for the purposes of encouraging members of the public to ask their doctors to prescribe a specific medicine. The Panel noted that the campaign was directed at health issues of the feet and/or toenails. None of the material provided to the public referred to any specific medicine. The material would increase the public's awareness and might encourage some people to visit their doctor to discuss possible treatment of fungal toenail infections but this was not necessarily unacceptable. Patients were not being encouraged to ask their doctor specifically for the company's product. It was not the only product to meet the treatment criteria given in the material. The Panel had ruled no breach of the Code. This had been upheld by the Appeal Board following an appeal by the complainant.

The Panel now turned to the case before it. The Panel noted the difference in wording between Clause 1.2 which listed what was not included in the definition of promotion, in relation to the term "specific medicines", and the use of the term "specific medicine" in Clause 20.2 of the Code. Clause 1.2 referred to "... no reference, either direct or indirect, to specific medicines" whereas Clause 20.2 referred to prescribing a "specific medicine" and dealt with information made available to the public which, if it referred to prescription only medicines, must not be promotional.

The Panel noted that the GH Therapy Update newsletter gave detailed information about treatment and, in the Panel's view, encouraged the use of growth hormone to treat adult growth hormone deficiency.

The Panel considered that the newsletter went further than the exemption given in Clause 1.2 which stated that the term promotion did not include statements relating to human health or diseases provided that there was no reference, either direct or indirect, to specific medicines. No products were mentioned by name but reference was made to growth hormone replacement therapy in adults and the benefits of such therapy. In the Panel's view the newsletter referred indirectly to specific medicines. The Panel considered that the nature of the material together with Pharmacia & Upjohn's involvement and commercial interest meant that the mailing in effect amounted to promotion of Pharmacia & Upjohn's growth hormone product - Genotropin. The Panel noted that this meant that prescribing information for Genotropin should have been included as required by Clause 4.1 of the Code.

The Panel noted that the back page of the newsletter stated that it had been published by Pharmacia & Upjohn and gave the company logo and address. The Panel did not consider that sponsorship of the newsletter was made sufficiently clear to those reading it. The newsletter looked as if it might have been produced independently, particularly as the editor's name appeared just below the title on the front page. The Panel considered that the declaration of sponsorship on the newsletter was not sufficiently clear and accordingly ruled a breach of Clause 9.9 of the Code.

The Panel noted that the covering letter from the

consultant endocrinologist made no mention of the fact that Pharmacia & Upjohn had produced and distributed the material. This was not in accordance with Clause 9.9 of the Code which required that all material relating to medicines and their uses that was sponsored by a pharmaceutical company must clearly indicate that it has been sponsored. A breach of Clause 9.9 was ruled. The Panel decided that the mailing as a whole constituted disguised promotion. The mailing purported to be educational material from a health professional but, in the Panel's view, the mailing was promotional. A breach of Clause 10.1 of the Code was ruled.

APPEAL BY PHARMACIA & UPJOHN

Pharmacia & Upjohn appealed against the Panel's ruling of a breach of Clause 10.1 of the Code. It considered that there were important issues involved which related to communication and liaison between the industry and the NHS. The healthcare environment in the UK was changing rapidly and healthcare providers were ever more demanding in their requests for up-to-date information and data relating to treatment and management of disease. Pharmacia & Upjohn believed that this case provided an opportunity for explanation and clarification of aspects of the Code which related to such communications.

In the Panel's response, two cases were quoted which it was stated "... raised similar issues ..." to this case. Pharmacia & Upjohn disagreed that there was, in fact, any such similarity. The first of these cases (AUTH/296/5/95) was ruled in breach of Clause 7.2 (lack of up-to-date information) and the second (AUTH/516/3/97) was ruled in breach of Clause 20.2 (information to the general public). There had never been any suggestion that the information contained within the GH Update was anything other than up-to-date and the independent editorial review by an eminent endocrinologist was enlisted precisely to ensure that this was the case. Also, Pharmacia & Upjohn stated in its original submission to the Panel that this material was only sent to health care professionals responsible for making NHS budgeting decisions. It was not sent to the general public. Pharmacia & Upjohn was concerned therefore that the true nature, context and use of its material had not been properly understood by the Panel and it did not understand the relevance of the two other cases quoted to its situation.

With regard to the specific findings, Pharmacia & Upjohn first dealt with the ruling of a breach of Clause 10.1. Once again, it questioned the relevance to this particular case of Clause 20.2, as discussed in the Panel ruling. It was Pharmacia & Upjohn's understanding that, pivotal to this finding, was the interpretation placed upon the terms "promotion" and "specific medicines" which appeared in Clause 1.2. The opinion of the Panel was that the material was promotional because a) it discussed the management of growth hormone deficiency in adults and b) the material was supported and provided by a company which supplied a treatment for this condition. This was interpreted by the Panel as reference to "specific medicines" and an encouragement to use growth hormone to treat adult growth hormone deficiency. Pharmacia & Upjohn had the following observations on this interpretation:

1 The material did not deal only with the treatment of adult growth hormone deficiency. It contained information on the prevalence, risks, diagnosis, and benefits of shared care. Indeed, as the Panel noted, it was clearly stated in the material that not all (50%) of those diagnosed, would require growth hormone treatment.

2 The Panel stated "No products were mentioned by name but reference was made to growth hormone replacement therapy in adults and the benefits of such therapy. In the Panel's view the newsletter referred indirectly to specific medicines."

An educational and informative document dealing with the condition of adult growth hormone deficiency, when discussing treatment, must address growth hormone replacement as it was currently the only treatment available. In addition to adult growth hormone deficiency, there were other conditions for which essentially only one treatment was available. Examples of such conditions might be insulin dependent diabetes mellitus (insulin treatment) and cardiovascular conditions requiring oral anticoagulation (warfarin treatment).

The logical extension of the Panel's decision was that it was not possible for any company which was involved in the supply of such treatments to support the production and supply of any material, including those listed in the final point of Clause 1.2, without that material becoming promotional in nature. Pharmacia & Upjohn requested clarification as to whether or not this was the intention of Clause 1.2 and also the opinion of the Appeal Board.

3 In the UK there were five growth hormone manufacturers, three of which were currently marketing the adult growth hormone deficiency indication. As the Panel had noted, no products were mentioned by name in this material. With reference to Pharmacia & Upjohn's comments and queries as set out in 2) above, it therefore also requested clarification of the term "specific medicines". Pharmacia & Upjohn believed that, as growth hormone replacement was the only treatment for adult growth hormone deficiency, and as it had deliberately avoided mentioning Genotropin by name, it was complying with both the letter and the spirit of Clause 1.2.

4 The intention of the material was to raise awareness and knowledge about a recently recognised condition which was currently acknowledged to be poorly understood. It was sent to healthcare professionals in the NHS who were responsible for budgetary planning and decision making. It was not sent to any person who was known to have any direct prescribing responsibility for growth hormone. Pharmacia & Upjohn therefore felt that the Panel's view that the material "encouraged the use of growth hormone to treat adult growth hormone deficiency", should be reviewed in this context, bearing in mind that, as stated above, growth hormone replacement was the only option currently available for the 50% of patients who could actually benefit clinically from pharmaceutical treatment.

In summary, Pharmacia & Upjohn believed that the material was consistent with the exemptions to the term "promotion" as set out in the final point of Clause 1.2 and therefore could not be deemed to constitute "disguised promotion" as set out in Clause 10.1.

Pharmacia & Upjohn noted the findings with regard to

breaches of Clause 9.9. It also noted the changes to the supplementary information to Clause 9.9 which appeared in the latest 1998 edition of the Code. The material in question was approved using the previous 1996 edition and, in the light of these changes to the Code, would have been amended to bring them into line anyway. Pharmacia & Upjohn therefore did not wish to appeal against the findings relating to breaches of Clause 9.9.

APPEAL BOARD RULING

The Appeal Board noted the previous cases referred to by the Panel, Cases AUTH/296/5/95 and AUTH/516/3/97. It considered that the previous cases were not irrelevant as they referred to the issue of what was meant by the terms "specific medicine" and "specific medicines".

The Appeal Board noted the exemption to the definition of promotion given in Clause 1.2 of the Code, for statements relating to human health or diseases provided there was no reference, either direct or indirect to specific medicines. The Appeal Board examined the material at issue and considered that it promoted growth hormone therapy as a class. The Appeal Board noted that there was more than one medicine within this class available on the UK market. It did not include any direct or indirect reference to a specific medicine as referred to in the exemption to the definition of promotion. It was therefore outside the definition of promotion. The mailing did not therefore constitute disguised promotion. The Appeal Board ruled no breach of Clause 10.1 of the Code.

The appeal was therefore successful.

Following its consideration of this case, the Appeal Board noted that the rulings of breaches of Clause 9.9 of the Code were appropriate as although the material was outside the definition of promotion, it still failed to meet the requirement that all material relating to medicines and their uses which was sponsored by a pharmaceutical company must clearly indicate that it had been sponsored by that company.

Complaint received **13 November 1997**

Case completed **25 February 1998**

CASE AUTH/645/11/97

SERONO v ORGANON

Puregon brochure

Serono complained about a scientific brochure for Puregon issued by Organon. It was alleged that the statement "A step-wise, gradually increasing dosage scheme is preferred, starting with 50 IU/day of Puregon for 7 to 14 days" was not in accordance with the product's marketing authorization. The summary of product characteristics (SPC) for Puregon stated "Anovulation: In general, a sequential treatment scheme is recommended. This usually starts with daily administration of 75 IU FSH activity." Serono was not aware of any published evidence demonstrating the safety and efficacy of a Puregon dosage of 50 IU in anovulation.

The Panel considered that it was misleading to specifically state in the scientific brochure that the starting dose in anovulation was 50 IU/day when the SPC stated that in general a sequential treatment scheme was recommended which usually started with 75 IU/day, and ruled that there had been a breach of the Code. The Panel noted that the SPC stated that studies had shown Puregon to be more effective than urinary FSH which suggested that a lower dose of Puregon might be appropriate and did not consider that the statement regarding the use of a 50 IU/day starting dose constituted promotion outside the marketing authorization.

Serono Laboratories (UK) Ltd submitted a complaint about the content of a scientific brochure (ref: 01420F) for Puregon distributed by Organon Laboratories Ltd.

The brochure was entitled "Puregon, Recombinant follicle stimulating hormone for the treatment of human infertility". Chapter 6 of the brochure was headed "Puregon, treatment in anovulatory infertility" and the complaint concerned a section headed "Dosing recommendations".

COMPLAINT

Serono alleged that the statement "A step-wise, gradually increasing dosage scheme is preferred, starting with 50 IU/day of Puregon for 7 to 14 days", was in breach of Clause 3.2 of the Code which required that the promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in its summary of product characteristics.

Serono pointed out that the summary of product characteristics (SPC) for Puregon stated that "Anovulation: In general, a sequential treatment scheme is recommended. This usually starts with daily administration of 75 I.U. FSH activity."

Serono was aware that it was appropriate to consider product claims in context, and had noted the use of the argument in the preceding paragraph to the statement at issue, that because Puregon had higher efficacy than urinary FSH it was appropriate to give lower doses of Puregon. Serono was aware that the phrase 'usually starts' formed part of the dosage wording.

Serono concluded that the advertised daily dose of 50 IU was inconsistent with the licensed dosage of 75 IU, in breach of Clause 3.2.

Serono was not aware of any published evidence demonstrating the safety and efficacy of a Puregon dosage of 50 IU in the clinical indication of anovulation. Serono stated that the same claim for 50 IU dose had been used in other advertising material for Puregon.

RESPONSE

Organon stated that it relied on two arguments. The first of these was based upon the requirement to advertise in accordance with the SPC, and the second upon the need to provide accurate information to medical practitioners.

1 Advertising in accordance with SPC

Firstly Organon emphasised that the wording in question appeared in a scientific brochure which contained about 40 pages of detailed technical information on Puregon. While such material was of course advertising, it was intended for limited distribution to a highly informed audience of specialists. It was not routine advertising material.

Secondly, Organon stated that the European Directive on advertising (92/28 EEC) required in Article 6, that "Any advertising of a medicinal product to persons qualified to prescribe or supply such products shall include: - Essential information compatible with the summary of product characteristics;...".

This wording was implemented in the Code as Clause 3.2. The wording in the Code emphasised that the promotion of a medicine must be "in accordance" with the terms of the marketing authorization (MA), and "not inconsistent" with it.

Organon confirmed that the MA for Puregon was a centralised MA, having been granted by the EC after a full review of all the scientific information, published and unpublished, by the Committee for Proprietary Medicinal Products (CPMP). The Puregon SPC was a part of the MA and had therefore been the subject of careful comment and approval by the CPMP.

Organon accepted that the SPC included dosage advice for treatment of anovulation in the posology section. However this advice was clearly preceded by some important "General" information on Puregon, and further general information on posology for this class of product. Organon stated that the dosing advice for Puregon therefore comprised three elements, presented, as requested by the CPMP, in the following order in the SPC: general advice on Puregon dosage, general advice on posology of gonadotrophins, specific advice on posology of Puregon.

General advice on Puregon dosage

Organon submitted that an assessment of the clinical documentation for Puregon during a centralised procedure, led the CPMP, and the Member States, to conclude that Puregon (follitropin beta, recFSH) was clearly, and statistically significantly, more active than urinary gonadotrophins. (Organon pointed out that superior efficacy to urinary gonadotrophins had not been demonstrated for the competitor recFSH follitropin alpha, marketed by Serono as Gonal F, a difference which may have led to the complaint).

Organon stated that the CPMP were so concerned about this increased activity of Puregon that it insisted that the following warning regarding dosage was added to SPC, and in a place preceding further dosage information:

"Posology and method of administration

General

The dosage recommendations given below are in line with those usually applied for urinary FSH. These dosages were also applied in comparative clinical studies with Puregon and urinary FSH. In these studies it was shown that Puregon is more effective than urinary FSH in terms of a lower total dose and a shorter treatment period needed to achieve pre-ovulatory conditions. Therefore, it may be appropriate to give a lower dosage of Puregon than for urinary FSH. This advice is not only relevant in order to optimise follicular development but also to minimise the risk of unwanted ovarian hyperstimulation. For this purpose the dosage range of Puregon includes the strengths of 50 I.U. and 100 I.U."

The CPMP advice reflected in the dosage warning, with which Organon, and medical practitioners were in complete agreement, had two strands; firstly that a lower dose of Puregon than urinary gonadotrophins might be required to optimise follicular development and secondly that a lower dose of Puregon than urinary gonadotrophins might be required in order to minimise the risk of ovarian hyperstimulation syndrome (OHSS), which might rarely be life-threatening.

General advice on posology of gonadotrophins

Organon submitted that it was well accepted in the field of infertility treatment that, for the reasons stated previously (optimisation of follicular development and minimisation of risk of OHSS), dose titration was essential in each patient. In the Puregon SPC, beneath the heading "Posology and method of administration" and following the general information referred to above, a heading "Posology" was followed by:

"There are great inter- and intra-individual variations in the response of the ovaries to exogenous gonadotropins. This makes it impossible to set a uniform dosage scheme. The dosage should, therefore, be adjusted individually depending on the ovarian response. This requires ultrasonography and monitoring of oestradiol levels.

After pituitary desensitisation induced by a GnRH agonist a higher dose of Puregon may be necessary to achieve an adequate follicular response".

Specific advice on posology of Puregon

Organon stated that having encountered these earlier warnings, the practitioner could now consider the following specific advice for Puregon, beneath the heading 'Anovulation' in the SPC:

"Anovulation

In general, a sequential treatment scheme is recommended. This usually starts with daily administration of 75 I.U. FSH activity. The starting dose is maintained for at least seven days. If there is no ovarian response, the daily dose is then gradually increased until follicle growth and/or plasma oestradiol levels indicate an adequate pharmacodynamic response. A daily increase of oestradiol levels of 40-100 per cent is considered to be optimal. The daily dose is then maintained until pre-ovulatory conditions are reached. Pre-ovulatory conditions are reached when there is ultrasonographic evidence of a dominant follicle of at least 18 mm in diameter and/or when plasma oestradiol levels of 300-900 picograms/ml (1000-3000 pmol/L) are attained. Usually, 7 to 14 days of treatment is sufficient to reach this state.

The administration of Puregon is then discontinued and ovulation can be induced by administering human chorionic gonadotropin (hCG). If the number of responding follicles is too high or oestradiol levels increase too rapidly, i.e. more than a daily doubling for oestradiol for two or three consecutive days, the daily dose should be decreased. Since follicles of over 14 mm may lead to pregnancies, multiple pre-ovulatory follicles exceeding 14 mm carry the risk of multiple gestations. In that case hCG should be withheld and pregnancy should be avoided in order to prevent multiple gestations."

In conclusion, Organon submitted that the dosage recommendations in the SPC clearly made provision for dosage adjustment, and in particular referred to the need for caution in view of the higher intrinsic activity of Puregon when compared to urinary gonadotrophins. Organon submitted that the wording in question reflected, and was consistent with, the information given in the SPC. As in the SPC, and reflecting the CPMP view of the efficacy of Puregon, it was prefaced at the beginning of the relevant section in the scientific brochure by an explanation of why a lower dose might be prudent.

2 Provision of accurate information to medical practitioners

Organon stated that the preamble to Directive 92/28/EEC admitted that advertising contributed to the information available to the prescriber. Furthermore Article 2 (3) required that the advertising of a medicinal product "...shall encourage the rational use of the medicinal product, by presenting it objectively and without exaggerating its properties, ...".

Organon stated that with the launch of follitropin beta (Puregon) it had not only launched a compound made by recombinant biotechnology but also introduced a paradigm shift in the clinician's approach to fertility treatment. When Bruno Lunenfeld first used urinary derived human menopausal gonadotrophins in the 1960s he suggested a starting dose of 75 IU, a dose which was then the content of a single ampoule. This concept of using fixed numbers of ampoules had proved very successful and had become entrenched in treatment protocols, so much so that clinicians spoke of ampoules instead of IUs. Organon stated that unfortunately, this simplistic approach did not take into consideration that fertility patients differed in their characteristics and requirements of FSH and may be graded into good, moderate and poor responders. The FSH requirement of patients at either end of the spectrum differed significantly. The danger with giving an unnecessary high dose of FSH to a woman with favourable prognostic indicators was multiple follicular genesis resulting in multiple births and all the sequelae related to this as well as ovarian hyperstimulation syndrome which might rarely be life threatening in a small number of cases.

Organon pointed out that these problems had recently been highlighted in a recent report from the Human Fertilization and Embryology Authority as well as in an article aimed at the general public (Time Magazine, 29 September 1997 entitled 'Baby, Baby Baby!'). "Fertility technology brings babies, but multiple births are straining both parents and health services."

Organon stated that it had contributed to transforming infertility management by challenging old fashioned concepts. The conclusions from the important paper 'Infertility Treatment: From Cookery to Science' in the British Journal of Obstetrics and Gynaecology November 1993 made the point that too little of fertility treatment was evidence-based. Here, Organon had led the way by undertaking the largest ever fertility studies which showed that follitropin beta was intrinsically more biologically active than urinary derived FSH. This was reflected in the cautionary wording in the SPC for Puregon. Opinion leaders in ovulation induction had already introduced the concept of a low starting dose in anovulatory women with polycystic ovarian disease. Therefore, for many of the leading clinics in the country, their normal protocols used a fraction of the 75 IU ampoule.

Organon stated that it was important that clinicians embarked on more 'physiological' fertility treatment regimens since these would not only produce good results but minimised side-effects. Puregon 50 IU presentation allowed for a flexible dosage administration which could be tailored to the individual. On the other hand the suggestion that treatment might be initiated with 50 IU of Puregon in no way implied that this dose was effective in all patients. On initiating therapy, and throughout treatment, the primary emphasis must be on patient safety. This was reflected in a cautious approach to therapy.

Organon believed that its approach to dosage advice for Puregon as published in the scientific brochure was consistent with the MA and SPC, and furthermore was consistent with the objectives of encouraging the safe and rational use of Puregon taking into account its increased efficacy compared to urinary gonadotrophins. Organon therefore denied a breach of the Code.

PANEL RULING

The Panel noted that, with regard to the specific dose of Puregon in anovulation, both the SPC and prescribing information (both of which were included in the scientific brochure) stated that "In general a sequential treatment scheme is recommended starting with daily administration of 75 IU". The Panel noted that, according to the SPC, this dose was in line with that usually applied to urinary FSH and was the dose used in comparative clinical studies with Puregon and urinary FSH. These studies had shown Puregon to be more effective than urinary FSH which suggested that a lower dose of Puregon might be appropriate.

The Panel noted that chapter 6 of the scientific brochure was entitled "Puregon treatment in anovulatory infertility". Under the heading of "Dosing recommendations" it was stated that "A stepwise gradually increasing dosing scheme is preferred, starting with 50 IU/day of Puregon...".

The Panel considered that it was misleading to specifically state in the scientific brochure that the starting dose of Puregon in anovulation was 50 IU/day when the SPC stated that in general a sequential treatment scheme was recommended which usually started with daily administration of 75 IU FSH activity and the prescribing information stated "starting with daily administration of 75 IU". The statement at issue in the scientific brochure

was not a fair reflection of the information given in the SPC regarding the dose of Puregon. A breach of Clause 7.2 was ruled.

The Panel did not consider that the statement regarding the use of a 50 IU starting dose constituted promotion of Puregon outside its marketing authorization given the additional information in the SPC. No breach of Clause 3.2 was ruled.

Complaint received 14 November 1997

Case completed 17 February 1998

CASE AUTH/646/11/97

GENERAL PRACTITIONER v SMITHKLINE BEECHAM

Offer of calendar

A general practitioner complained about a reply paid card from SmithKline Beecham which offered a desk-top calendar. The complainant alleged that the statement "I understand that a representative will deliver this item" was an inducement to gain an interview since receiving the calendar was dependent on seeing a representative. A space was provided on the card for the doctor to complete to indicate the day and time that would be most convenient.

The Panel considered that doctors receiving the mailing would most likely gain the impression that they were obliged to see a representative in order to receive a calendar. This would be unacceptable under Clause 15.3 as it would have been used as an inducement to gain an interview but there was no evidence that this had actually happened. The Panel ruled a breach of Clause 9.1 of the Code because the wording of the card meant that the company had failed to maintain high standards.

Upon appeal by SmithKline Beecham, the Appeal Board considered that readers would assume that to receive the calendar they were obliged to see the representative and this was unacceptable. The Appeal Board considered, however, that the appropriate ruling was of a breach of Clause 15.3.

A general practitioner complained about a reply paid card (ref 1097 FM:RC/7/06/1) provided by SmithKline Beecham Pharmaceuticals as part of a "Dear Doctor" mailing on Famvir. The reply-paid reply card was headed "I would like to receive a complimentary 1998 "wonders of the world", desk-top calendar" beneath which there was a box for the doctor to tick. This was followed by the statement "I understand that a representative will deliver this item". A space was provided for the doctor to complete to indicate the day and time that would be most convenient. The doctor's name and address appeared on the card.

COMPLAINT

The complainant alleged that the statement "I understand that a representative will deliver this item" was an inducement to gain an interview since receiving the item was dependent upon seeing a representative.

RESPONSE

SmithKline Beecham acknowledged that the card stated that a representative would deliver the item. It was company policy not to send such materials by post, therefore representatives hand delivered all items to surgeries. The company submitted that when possible the representative would offer to give the items directly to the doctor. However, should this be inconvenient the representative would leave the item at the surgery reception.

The company submitted that its representatives routinely used cards similar to the one at issue and the representatives were familiar with the Code. All representatives were given induction training on the Code on joining the company and ongoing training. The representatives were aware that inducement or subterfuge to gain an interview was unacceptable.

The company did not consider that the card could any way be construed to cause offence in terms of suitability and taste, neither did it in any way denigrate the professional standing of the audience. The cost of each calendar was £1.32.

PANEL RULING

The Panel noted that the reply paid card for the doctor to complete stated that a representative would call to deliver the calendar. This was followed by a request for the doctor to indicate the day and time that would be most convenient.

The Panel accepted that items offered on mailings were often delivered by representatives and this was not unacceptable in principle. However, even if a mailing stated that a representative would call to deliver a requested item, if the doctor was not available to see the representative then the item had to be left for the doctor as it otherwise became an inducement to gain an interview.

The Panel examined the wording of the reply paid card. It considered that doctors receiving the mailing would most likely gain the impression that they were obliged to make an appointment to see the representative in order to receive the calendar. This would be taken to be the reason for the doctor having to fill in a date and time that would be convenient. This was unacceptable under Clause 15.3 of the Code as the calendar would have been used as an inducement to gain an interview. There was no evidence that this had actually happened. The company was, however, at fault for the wording of the reply paid card. The Panel considered that the wording of the reply paid card meant that SmithKline Beecham had failed to maintain a high standard. The Panel therefore ruled a

breach of Clause 9.1 of the Code.

APPEAL BY SMITHKLINE BEECHAM

SmithKline Beecham said that it did not believe that it was in breach of Clause 9.1 and had appealed for the following reasons:

1 The wording adopted by SmithKline Beecham was widely used within the industry.

2 SmithKline Beecham did not believe that this wording could be misinterpreted as subterfuge or an inducement to gain an interview.

3 SmithKline Beecham did not accept that it had in any way failed to maintain a high standard.

SmithKline Beecham submitted copies of reply paid cards from three other companies, stating that it was clear to it that the use of reply paid cards with similar wording to the one subject to the appeal was widespread. It was therefore a standard industry practice. Unless it was believed that a large number of companies were also guilty, SmithKline Beecham believed that it had not been guilty of failing to maintain a high standard.

APPEAL BOARD RULING

The Appeal Board examined the reply paid card in question together with the reply paid cards from other companies that had been provided by SmithKline Beecham. The reply paid card in question stated that "I understand that a representative will deliver the item". This was immediately followed by a request of the doctor to indicate which day and time would be most convenient. The three examples provided by SmithKline Beecham used phrases such as "Please arrange for me to receive", "I would like to request" and "I would like to receive" followed by a space for the doctor to indicate the best time and day to visit or call. None of the examples provided expressly stated that a representative would deliver the item.

The Appeal Board considered that the wording and layout of the card in question was such that readers would assume that in order to receive the calendar they were obliged to see the representative. This was unacceptable. The Appeal Board did not understand why the Panel had ruled a breach of Clause 9.1 of the Code. It considered that Clause 15.3 of Code was the more appropriate clause as the sender of the card, in effect, was an agent of the representative. The Appeal Board ruled a breach of Clause 15.3 of the Code and no breach of Clause 9.1.

The appeal therefore failed.

Complaint received **14 November 1997**

Case completed **1 April 1998**

CASE AUTH/647/11/97

NO BREACH OF THE CODE

GLAXO WELLCOME v ZENECA

Promotion of Zomig

The Medicines Control Agency (MCA) referred to the Authority a complaint which it had received from Glaxo Wellcome about the promotion of Zomig by Zeneca. As the complaint primarily concerned the activities of representatives the MCA considered it would more suitably handled by the Authority.

Glaxo Wellcome alleged that Zeneca representatives were promoting the use of Zomig for the treatment of migraine in adolescents. It had received feedback from various health professionals that it was so recommended and this had been confirmed at a recent open meeting attended by both Glaxo Wellcome and Zeneca representatives. The summary of product characteristics (SPC) for Zomig stated that its safety and efficacy had not been established in paediatric patients and no age range was included to define paediatric. Data obtained from Zeneca stated that although adolescent patients aged 12-17 had been included in some studies, there were insufficient numbers for a formal statistical analysis. Zeneca had also stated that there was no bar to the use of Zomig in children over the age of 12. Glaxo Wellcome was concerned that Zeneca was promoting Zomig for an age group for which statistically significant efficacy data were not available.

The Panel observed that the Zomig SPC did not mention adolescent patients but did state that its safety and efficacy in paediatric patients had not been established. The Panel noted Zeneca's statement that it had not been actively promoting the use of Zomig in adolescents. The product's briefing material for representatives did not refer to its use in adolescents though it did mention that Glaxo Wellcome's Naramig was not recommended in patients under 18. The Panel considered that there was no evidence that Zeneca representatives had promoted Zomig for use in adolescents. It was likely that representatives would be asked about the matter but a simple statement of fact consistent with the product licence was not unreasonable as a response, though the Panel considered that the representative briefing material could have been more helpful on the point. No breach was ruled.

The Medicines Control Agency (MCA) referred a complaint it had received from Glaxo Wellcome UK Limited regarding the promotion of Zomig by Zeneca Pharma. The MCA considered that as the complaint referred primarily to the activities of company representatives it would be more suitably handled by the Authority. The complaint had been referred to the Authority in accordance with Regulation 5 of the Medicines (Monitoring of Advertising) Regulations 1994 (SI 1994 No. 1933).

The Authority advised both Glaxo Wellcome and Zeneca that it was disappointed that Glaxo Wellcome had not referred the matter directly to the Authority.

COMPLAINT

Glaxo Wellcome had written to the Medicines Control Agency (MCA) raising several points concerning the promotion of Zomig in adolescents by Zeneca Pharma.

It had come to Glaxo Wellcome's attention that Zeneca representatives were promoting the use of Zomig for the treatment of migraine in adolescents. The company was not aware of any written promotional material on the issue. It had received feedback from various healthcare professionals across the country that Zomig was recommended for adolescents. This had been confirmed at a recent open meeting attended by both Glaxo Wellcome and Zeneca representatives.

Glaxo Wellcome referred to the Zomig summary of product characteristics (SPC) which stated that the safety and efficacy of Zomig had not been established in paediatric patients and no age range was included to define paediatric. A Glaxo Wellcome employee contacted the medical information department at Zeneca to request data which supported the efficacy claim for adolescents. A copy of the response dated 9 October 1997 was provided. It stated that although patients aged 12-17 years were included in some clinical studies, insufficient numbers were recruited to prepare a formal statistical analysis. Glaxo Wellcome also provided a copy of a second letter from Zeneca (dated 25 July 1997) which stated that there was no bar to the use of Zomig in children over the age of 12 years.

Glaxo Wellcome was concerned that Zeneca was promoting Zomig in an age group for which statistically significant efficacy data were not available. The company stated that even though the wording in the dosage section of the Zomig SPC did not specifically preclude adolescents it welcomed the MCA's comments on the appropriateness of promoting the use of this product in this age group given the lack of supporting data.

RESPONSE

Zeneca submitted that it had not been actively promoting the use of Zomig in adolescents. The company had no promotional material which made any reference to the use of Zomig in adolescents nor had it produced any such material. Furthermore Glaxo Wellcome had stated that it was not aware of any such promotional material.

The only occasion when a Zeneca representative was likely to discuss the use of Zomig in adolescents was in response to a direct question from a health professional. Zeneca said its position was clearly stated in the letter to Glaxo Wellcome of 9 October 1997. This letter, which was accompanied by confidential data on file, stated that initially the Zomig clinical trial programme required patients to be at least 18 years old. Subsequent studies permitted patients aged 12 years and over to be entered into controlled and open studies. However only a small number of adolescents was recruited and as such was insufficient to prepare a formal statistical analysis. The efficacy (headache response rate) quoted for placebo controlled trials included patients aged 12 to 18 years. A small number entered an open label study which assessed the long term efficacy of Zomig 5mg (with an option to use a further 5mg for recurrence). The headache response rate at two hours post dose in the small group (achieved

in 62% of attacks) was comparable to the two hour headache response rates found in single attack studies (62-65% with Zomig 2.5mg and 62-67% with Zomig 5mg) in a trial population aged 12-65. There were no apparent safety concerns in the pattern or severity of adverse events in the adolescents treated with Zomig. The licensing authority had not asked Zeneca to formally exclude adolescents in the SPC for Zomig.

Zeneca submitted that as migraine was a condition that might emerge during adolescence and which could be refractory to therapy, it was likely that Zeneca representatives would on occasion be asked about the use of Zomig in these patients. A response to such an enquiry along the lines of the Zeneca letter to Glaxo Wellcome was a simple statement of the facts consistent with the product licence. The company had no evidence nor any reason to believe that its representatives were stating anything else when questioned.

Zeneca pointed out that Glaxo Wellcome in its complaint to the MCA failed to provide any evidence to support the allegation. Should Glaxo Wellcome have any evidence of a Zeneca representative making inappropriate claims, the company would like to have sight of it. Glaxo Wellcome had also referred to a recent open meeting but neither identified the meeting nor stated what had happened. Should Glaxo Wellcome care to identify the meeting the company would be pleased to respond to any issues raised in connection with it.

Zeneca provided copies of the representatives' briefing materials which it requested were not passed to Glaxo Wellcome. There were three items. Firstly, promotional notes dated April 1997 which set out the promotional strategy and materials for the launch of Zomig and its subsequent promotion. Zeneca pointed out that there was no reference to the use of Zomig in adolescents as this was not part of the promotional strategy. Secondly, a "Staying Ahead of the Competition" folder. Following the launch of Glaxo Wellcome's product Naramig, a single copy of the folder was sent to each representative. The folder contained a Naramig SPC, briefing notes dealing with claims made by Glaxo Wellcome for Naramig and a Naramig "Objection handler" which emphasised the main promotional claims for Zomig and highlighted the two main differences between the Naramig SPC and the Zomig SPC. These being contraindications on the Naramig SPC relating to the product's use in adolescents and the taking of a second dose. The folder listed the key communication messages for Zomig and instructed the representatives to stick closely to them. Zeneca pointed out that the use of Zomig in adolescents was not one of the messages. The third item was a briefing note dated 14 October to representatives from the product manager and the medical adviser reminding representatives of the marketing strategy and promotional claims. Zeneca pointed out that use in adolescents was not part of the promotional campaign.

In conclusion Zeneca believed that its representatives were not promoting Zomig in a manner inconsistent with the product licence and not making any claims which were either misleading or not capable of substantiation. It submitted that its representatives had at all times maintained a high standard of ethical conduct and on this occasion had dealt with the enquiries on Zomig in a proper manner.

PANEL RULING

The Panel noted that the Zomig SPC did not mention adolescent patients. Reference was made to patients aged over 65 and with regard to use in children the SPC stated that the safety and efficacy of Zomig in paediatric patients had not been established. In the Panel's view it was clear that the product was not indicated for use in paediatric patients. The SPC was silent as to whether the product could be used in adolescent patients. The Panel considered that just because the SPC did not prohibit use of Zomig in adolescent patients it did not necessarily mean that the product could be actively recommended for use in this patient group.

The Panel examined the Naramig SPC dated April 1997 which appeared in the ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1998-99. The SPC gave the dose of Naramig for adults (18-65 years of age). The SPC stated that in adolescents (12-17 years of age) the efficacy of Naramig at single doses of 0.25, 1.0 and 2.5mg was not demonstrated to be greater than placebo and therefore the use of Naramig in patients under 18 years of age was not recommended. The SPC also stated that in children (under 12 years of age) and in the elderly (over 65 years of age) the use of Naramig could not be recommended.

The Panel noted that the Naramig SPC gave more detailed instructions about the various age groups than the Zomig SPC. The Panel noted that Zeneca had limited data on the treatment of 74 migraine attacks in 13 patients between the ages of 12 and 18.

The Panel noted Zeneca's response that it had not been actively promoting the use of Zomig in adolescents and that the only occasion when a Zeneca representative was likely to discuss the matter was in response to a direct question from a health professional.

The Panel noted that part of the representatives' briefing material referred to the fact that Naramig was not recommended in patients under 18 years of age. There was no mention that use of Zomig in adolescents was part of the promotional strategy for the product. The Panel considered that it would have been helpful if the Zeneca representatives had been given more explicit instructions about the use of Zomig in adolescents. In particular it might have been helpful to stress that the representatives were not to raise the subject but could answer unsolicited questions or refer questions to the medical information department.

The Panel considered that on balance there was no evidence that Zeneca representatives had promoted Zomig for use in adolescent patients. Insufficient details had been provided by Glaxo Wellcome. The Panel considered that, given the statement on the Naramig SPC regarding the use of the product in adolescents, it was likely that Zeneca representatives might be asked about the use of Zomig in these patients. If the representatives had responded to such unsolicited enquiries from health professionals as outlined by Zeneca then this was not unreasonable bearing in mind that there was some, albeit limited, relevant data. The Panel therefore ruled no breach of Clauses 3.2 and 15.2.

Complaint received **14 November 1997**

Case completed **19 February 1998**

CASE AUTH/648/11/97

SMITHKLINE BEECHAM v LILLY

Prozac advertisement

SmithKline Beecham complained about a journal advertisement for Prozac (fluoxetine) issued by Lilly alleging that the advertisement implied that the occurrence of discontinuation symptoms after cessation of an antidepressant was highly clinically relevant. SmithKline Beecham did not consider this to be so. The advertisement gave an unfair and unbalanced picture of the clinical relevance of this phenomenon.

The Panel observed that the advertisement focused only on discontinuation syndrome. The Panel noted that the Code did not preclude the promotion of a particular quality of a medicine, as opposed to its overall clinical profile. The Panel considered that the advertisement was not unreasonable and did not accept that it gave an unfair and unbalanced picture of the clinical relevance of discontinuation syndrome. No breach of the Code was ruled.

SmithKline Beecham further alleged that the claim "So Prozac makes it easy for you and your patients on stopping treatment or if therapy is interrupted" was misrepresentative. It did not take into consideration the difficulties caused by the long half-life of fluoxetine and its active metabolite norfluoxetine which meant that active medicine might remain in the body for up to three months. They could not be cleared quickly from the body and interactions could occur several weeks after discontinuation.

The Panel noted that the claim in question was preceded by two positive claims about Prozac and discontinuation syndrome. It considered that the claim created the impression that there were no unfavourable consequences associated with the long half-life and this was not so. The claim was too general and therefore misleading and was ruled in breach.

SmithKline Beecham Pharmaceuticals submitted a complaint about a journal advertisement for Prozac (fluoxetine), (reference PZ 938), issued by Eli Lilly & Company Limited. The advertisement was headed "True leadership has to be earned" and had the subheading "Reducing the risk of discontinuation syndrome", beneath which appeared the following claims. "Prozac is rarely associated with unpleasant antidepressant discontinuation symptoms. Prozac's long half-life may protect against such symptoms. So Prozac makes it easy for you and your patients on stopping treatment or if therapy is interrupted." These were given as "Possible reasons why Prozac has earned its status around the world".

SmithKline Beecham alleged that the advertisement in its entirety was unbalanced and misleading as it exaggerated the clinical importance of discontinuation symptoms in the management of depression and anxiety disorders and implied that these symptoms did not occur with fluoxetine.

1 Clinical relevance of discontinuation syndrome

COMPLAINT

SmithKline Beecham stated that the advertisement implied that the occurrence of discontinuation symptoms after cessation of an antidepressant was highly clinically relevant. SmithKline Beecham did not consider this to be so.

SmithKline Beecham stated that discontinuation events were not a new phenomenon, and were first reported in the late 1950s to occur on abrupt cessation of psychoactive medicines. These symptoms were frequently seen with tricyclic antidepressants (TCAs) and the incidence was generally thought to be in the range of 21-55%. The symptoms seen with TCAs were similar to those seen with selective serotonin reuptake inhibitors (SSRIs), although they seemed to occur less frequently with SSRIs.

SmithKline Beecham stated that discontinuation symptoms could be minimised by gradually tapering the dose, as recommended in the British National Formulary (BNF) for all psychoactive medications. With dose tapering, symptoms following SSRI discontinuation were generally mild, transient and resolved without intervention usually within 6-10 days, which represented only a short period of time during the management of a patient's depression/ anxiety.

SmithKline Beecham stated that the most important factor in choosing an antidepressant was a consideration of whether the overall profile of the medicine best suited the individual patient's needs. The implication was that fluoxetine was a superior antidepressant based entirely on its reported rate of discontinuation events and did not take into account the medicine's overall profile.

Discontinuation events could occur several weeks after stopping treatment and had been reported to persist for up to 2 months. Because of the delay in onset, patients and physicians might not associate these events with the termination of treatment which might lead to failure to report the condition. The symptoms might also be mistakenly diagnosed as a relapse of depression, leading to the patient being inappropriately treated with a further course of an antidepressant.

In addition, highlighting the occurrence of discontinuation syndromes in this way might lead to confusion amongst doctors that these symptoms were due to dependence or addiction, as seen on withdrawal of benzodiazepines. In contrast, symptoms seen with SSRIs had not been associated with dependence, and patients did not exhibit such behaviour as medication tolerance, craving, drug-seeking behaviour or self-neglect.

SmithKline Beecham alleged that the advertisement gave an unfair and unbalanced picture of the clinical relevance of this phenomenon and was misleading as regards to the properties of SSRIs and other antidepressants and that the entire content of the advertisement was in breach of Clause 7.2 of the Code.

RESPONSE

a) Evidence about antidepressant discontinuation

Lilly stated that the phenomenon had been the subject of several reports in recent years (Lejoyeuz and Ades (1997)). It had been brought to medical attention in many different ways:

Reports to the Committee on Safety of Medicines

In 1993 the Committee on Safety of Medicines issued a report on withdrawal symptoms with paroxetine (a copy was provided). The report described symptoms reported in 78 cases following withdrawal of paroxetine. Symptoms included dizziness, sweating, nausea, insomnia, tremor and confusion.

Lilly stated that Price *et al* (1996) calculated the frequency of reports to the Committee on Safety of Medicines of withdrawal phenomena associated with SSRIs as follows: fluoxetine, 0.002 per thousand prescriptions; fluvoxamine and sertraline, 0.03 and paroxetine, 0.3.

Case reports in the literature

Lilly stated that Barr *et al* (1994) reported 3 patients out of 6 who experienced symptoms on discontinuation of paroxetine following a 12 week trial for treatment of obsessive compulsive disorder. Symptoms occurred in these patients following cessation of paroxetine after a 7 to 14 day taper of the dose. Frost and Lal (1995) described 3 cases of shock like sensations after discontinuation of SSRIs. Two of their patients experienced these symptoms after cessation of paroxetine and one after sertraline. Bloch *et al* (1995) described 2 cases of severe psychiatric symptoms associated with paroxetine withdrawal. Berlin (1996) described 3 cases of dizziness and "light headedness" following fluoxetine withdrawal.

Retrospective study of clinic attenders

Lilly stated that Coupland *et al* (1996) reported the rates of symptoms experienced in 171 outpatient clinic attenders who were supervised during antidepressant tapering and discontinuation. They defined cases as patients who experienced at least one new symptom during discontinuation. Recurrences or exacerbation of pre-existing symptoms was not sufficient to define a case. Lilly stated the frequency of cases as reported in the paper was clomipramine 30.8%; paroxetine 20%; fluvoxamine 14%; sertraline 2.2% and fluoxetine 0%.

Clinical trial data

Lilly stated that after completion of a 12 week, double-blind study of treatment of panic disorder involving 120 patients, 34.5% of patients experienced discontinuation symptoms after abrupt cessation of paroxetine compared to 13.5% of those discontinued from placebo, Oehrberg *et al* (1995). The symptoms were rated as of moderate or mild severity. In a randomised placebo controlled study, clinically significant withdrawal symptoms did not occur after abrupt substitution of placebo for fluoxetine compared to continuing fluoxetine (Michelson (1997)).

Literature reviews

Lilly stated that Haddad (1997) contrasted the low frequency with which discontinuation reactions were found in clinical trial databases held by pharmaceutical companies with the high frequency found in clinical studies specifically designed to investigate discontinuation reactions. He suggested three reasons for this: Firstly that discontinuation reactions rarely occurred in patients who had received fewer than 8 weeks of treatment with an SSRI, yet clinical trials were often shorter than this. Secondly that clinical trials seldom included follow-up data after cessation of medication and thirdly that It was probable that discontinuation symptoms were more common following cessation of high doses of SSRIs, but clinical trials often used relatively low doses.

Haddad (1997) also reported seven published studies which had been specifically designed to assess discontinuation symptoms. He noted that they all reported "clinically significant rates (ie, 20% and upward) of discontinuation symptoms, at least for some SSRIs".

In a review of the literature of antidepressant discontinuation (Lejoyeux and Ades (1997)) it was concluded that symptoms were more common after discontinuation of a shorter acting SSRI such as paroxetine than with fluoxetine.

Doctors' knowledge of antidepressant discontinuation symptoms

Lilly stated that Young and Currie (1997) investigated the knowledge of psychiatrists and general practitioners about antidepressant discontinuation symptoms. They found that 94% of psychiatrists and 68% of general practitioners were aware of SSRI discontinuation symptoms and 66% of psychiatrists and 42% of practitioners had seen such patients. Approximately 50% of both groups usually advised patients of the possibility of such symptoms with fewer indicating that they would report such events to a national database.

Definition of a SSRI discontinuation syndrome

Lilly stated that due to the increasing frequency of reports of SSRI discontinuation symptoms, Shatzberg *et al* (1997) proposed a definition of a SSRI discontinuation syndrome. This was provided.

Lilly submitted that in the light of the above evidence it was clear that SSRI discontinuation symptoms were of clinical relevance and of potential concern to patients and the medical professionals treating them.

b) SmithKline Beecham's assertions about antidepressant discontinuation

Lilly stated that SmithKline Beecham, despite its assertion that it did not consider discontinuation symptoms to be clinically relevant, expressed contrary sentiments and quoted from SmithKline Beecham's letter:

"Because of a delay in onset, patients and physicians may not associate these events with the termination of treatment which may lead to failure to report the condition. The symptoms may also be mistakenly diagnosed as a relapse of depression, leading to the patient being inappropriately treated with a further course of antidepressant".

Lilly was in agreement with SmithKline Beecham that discontinuation symptoms might frequently not be recognised as medication related events and they might

be misdiagnosed as a relapse of depression. Since SmithKline Beecham had made such a statement it was difficult to understand why the company believed that SSRI discontinuation symptoms were not clinically relevant.

Lilly noted that SmithKline Beecham had cited the BNF recommendations for dose tapering. If discontinuation symptoms were not clinically relevant there would be no need for such recommendations in the BNF. Lilly agreed that dose tapering was important to minimise the risk of symptoms, particularly for patients who had been taking short half-life SSRIs for protracted periods. A slow taper was not required for most patients discontinuing fluoxetine, due to its long half-life (Stokes, 1993) which might provide protection against discontinuation symptoms, Rosenbaum and Zajecka (1997).

c) The advertisement's portrayal of antidepressant discontinuation and fluoxetine

Lilly did not agree with SmithKline Beecham's assertion that the advertisement implied that fluoxetine was a superior antidepressant based *entirely* on its reported rate of discontinuation events. Individual characteristics of fluoxetine were addressed in different, separate advertisements for the product. The advertisements shared the theme of leadership, based on the fact that fluoxetine was the first SSRI antidepressant to be marketed and was currently the most widely prescribed antidepressant brand in the world. Each advertisement highlighted a different, positive characteristic of fluoxetine (eg low rate of adverse events, efficacy in treating anxiety associated with depression, reducing risk of discontinuation syndrome). Lilly made no claim that it was because of any single one of these features that fluoxetine maintained its market leading position. In each of the advertisements it suggested that the feature highlighted provided a possible reason why fluoxetine had earned this status.

Lilly strongly rejected the implication that the advertisement suggested that discontinuation symptoms were related to dependence or addiction. It agreed that antidepressant discontinuation syndrome was unrelated to dependence or addiction. Price *et al* (1996) made the point that symptoms on withdrawal of antidepressants were not related to physical drug dependency syndrome. The definition of the discontinuation syndrome (Schatzberg (1997)), made it clear that the phenomena of the syndrome were different from those of withdrawal from a dependence producing medicine. Since Young and Currie (1997) found that 94% of psychiatrists and 68% of general practitioners were aware of SSRI discontinuation symptoms, it did not agree with SmithKline Beecham's assertion that its advertisement would lead to confusion amongst doctors that these symptoms were due to drug dependence.

Lilly submitted that the advertisement fairly reflected the literature on antidepressant discontinuation as it pertained to fluoxetine. The company did not agree with SmithKline Beecham's assertion that it was unbalanced, misleading, exaggerated the clinical importance of discontinuation symptoms or implied that these symptoms did not occur with fluoxetine. There was no basis to its claim that the advertisement was "misleading as regards to the properties of SSRIs and other antidepressants". The advertisement dealt with the properties of fluoxetine in relation to discontinuation symptoms. No comparisons between fluoxetine and any other product were made in the advertisement and there was no reference to other SSRIs or other antidepressants.

PANEL RULING

The Panel noted that the advertisement at issue focused only on discontinuation syndrome. The Panel noted that the Code did not preclude the promotion of a particular quality of a medicine, as opposed to its overall clinical profile, providing such promotion complied with the Code.

The Panel considered that the advertisement in question was not unreasonable. It did not accept that the advertisement gave an unfair and unbalanced picture of the clinical relevance of discontinuation syndrome. The Panel ruled no breach of Clause 7.2 of the Code in this regard.

2 Claim "So Prozac makes it easy for you and your patients on stopping treatment or if therapy is interrupted".

COMPLAINT

SmithKline Beecham submitted that this was misrepresentative as it did not take into consideration the difficulties caused by the long half-life of fluoxetine.

SmithKline Beecham stated that the long half-life of fluoxetine (4-6 days) and of its active metabolite norfluoxetine (4-16 days), meant that active medicine might remain in the body for up to 3 months (5 times the half-life). This meant that in the event of a patient requiring abrupt discontinuation of therapy, fluoxetine/norfluoxetine could not be cleared from the body rapidly.

SmithKline Beecham submitted that patients and healthcare workers also needed to be aware of the possibility of serious interactions with other medicines which might occur several weeks after fluoxetine had been discontinued. Indeed, the fluoxetine data sheet included a warning about the possibility of an interaction with other medicines metabolised by the hepatic cytochrome P450IID6 isoenzyme system if fluoxetine had been taken within the previous 5 weeks.

SmithKline Beecham stated that the possibility of an interaction might restrict the use of further antidepressant therapy, eg at least 5 weeks should elapse between discontinuation of fluoxetine and initiation of therapy with a monoamine-oxidase inhibitor.

SmithKline Beecham therefore did not agree with the claim "...Prozac makes it easy for you and your patients on stopping treatment..." and alleged it was misleading in breach of Clause 7.2 of the Code.

RESPONSE

Lilly noted that SmithKline Beecham considered that the statement "...Prozac makes it easy for you and your patients on stopping treatment..." was misrepresentative.

Lilly submitted that SmithKline Beecham had taken the claim out of context. The sentence occurred in the context of the remainder of the advertisement which dealt with fluoxetine and its relationship to discontinuation symptoms. It was the third in a sequence of statements that followed on from one another. All claims were substantiated by studies or papers to which they were referenced. The claim in question was referenced to Stokes (1993) who stated:

"Unlike TCAs, even the abrupt discontinuation of fluoxetine does not typically result in unpleasant withdrawal symptoms. The extended half-lives of fluoxetine and its metabolite, norfluoxetine, result in gradual reduction in drug activity. Thus for most patients there is no need to institute a series of gradual dose reductions".

Therapy interruption was referenced to Lilly data on file. This was a study that showed no significant change in reporting of adverse events or severity of depressive symptoms in patients whose treatment with fluoxetine was interrupted for a period of 5 to 8 days. In contrast, patients taking the SSRIs sertraline and paroxetine who had similar interruptions of their medication experienced increased numbers of adverse events and breakthrough of depressive symptoms.

The length of the half-life of any drug was a feature of its pharmacokinetics which might confer advantages and disadvantages depending on the circumstances in which it was being used. In the context of this advertisement which addressed the issue of discontinuation symptoms, Lilly considered that it was justified to highlight this advantage of the long half-life of fluoxetine.

Lilly noted the disadvantages of the long half-life of fluoxetine were not ignored but were included in the prescribing information in the advertisement. SmithKline Beecham raised the issue of the half-life of fluoxetine in relation to serious interactions with other medicines, allergic reactions and unexpected pregnancy. Lilly stated that these needed to be seen in context and would be addressed in turn.

Interactions with other medicines

Lilly stated that a clear warning was given in the Prozac data sheet of the medicines with which there might be an interaction. Such medicines were likely to be prescribed only if the prescribing doctor felt the risk to be justified and were likely to be introduced cautiously. If an interaction with one of these medicines was to occur and the medicines were then withdrawn, the duration of the interaction would depend on the clearance of the shorter acting compound. Lilly submitted that in this context the half-life of fluoxetine had little relevance.

Allergic reactions

Lilly stated that allergic reactions were not predictable but their occurrence was rare. Out of approximately three million patients prescribed fluoxetine in the UK up to 21st November 1997, the Committee on Safety of Medicines had received the following reports of allergic reactions:

Allergic reaction (non-specific) 20, anaphylactic reaction 7, serum sickness 1, Stevens-Johnson syndrome 2.

Despite the theoretical prolongation of such reactions with a longer half-life medicine, Lilly was unaware of cases where this had been reported. It noted that SmithKline Beecham raised this as a theoretical possibility but did not substantiate this risk by reference to reported cases.

Unexpected pregnancy

Lilly maintained a worldwide fluoxetine pregnancy register to monitor the outcomes of fluoxetine exposed pregnancies. Outcomes of pregnancies of women who were exposed to fluoxetine in the first trimester had been examined for 796 pregnancies (Goldstein *et al* (1997)). Spontaneous abortion occurred in 13.3% of the pregnancies which compared with historic assessments estimating spontaneous abortion in 15% of recognised pregnancies. In the remaining pregnancies, major malformations occurred in the infant in 3.5%. This rate was consistent with the expected 4% rate in the general population. Though caution was recommended regarding use of fluoxetine in pregnancy such information meant that the risk was not entirely unknown and allowed doctors and their patients to weigh risks and benefits based on evidence.

Lilly did not consider that addressing the issue of SSRI discontinuation symptoms distorted or exaggerated their clinical relevance as suggested by SmithKline Beecham. Of the SSRI anti-depressants, paroxetine, a product of SmithKline Beecham had been the most frequent subject of reports to the Committee on Safety of Medicines and symptoms occurring on withdrawal (Price *et al* (1996)). Lilly submitted that it might be that this influenced SmithKline Beecham's wish to minimise the clinical relevance of the issue. Since fluoxetine had the lowest reported rate of occurrence of discontinuation symptoms amongst the SSRIs (Price et al (1996); Haddad, (1997), Lilly submitted that it was legitimate to publicise this clinical advantage in its promotional material.

PANEL RULING

The Panel noted that the claim, "So Prozac makes it easy for you and your patients on stopping treatment or if therapy is interrupted", was preceded by two positive claims about Prozac and discontinuation syndrome. The Panel considered that the claim created the impression that there were no unfavourable consequences associated with the long half-life of Prozac and this was not so.

The Panel noted that whilst information regarding discontinuation of Prozac was given in the prescribing information, it was an accepted principle of the Code that material could not be qualified by way of a footnote or in the prescribing information. The Panel considered that the claim was too general and was therefore misleading. The Panel ruled a breach of Clause 7.2 of the Code.

Complaint received **20 November 1997**

Case completed **19 February 1998**

CODE OF PRACTICE REVIEW - MAY 1998

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

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).