PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

NUMBER 18 NOVEMBER 1997

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

Revised Code of Practice agreed

At the Half-Yearly General Meeting of The Association of the British Pharmaceutical Industry (ABPI) in October, member companies agreed changes to the Code of Practice for the Pharmaceutical Industry.

The British Medical Association, the Medicines Control Agency, the Office of Fair Trading and the Royal Pharmaceutical Society of Great Britain were all consulted about the changes, as were members of the ABPI and those companies which, though not members of the ABPI, have nonetheless agreed to comply with the Code and accept the jurisdiction of the Authority.

Brief details of the changes are set out overleaf. Copies of the 1998 edition of the Code will be available before the end of the year.

New Secretary appointed

Etta Logan has been appointed as Secretary to the Authority by the ABPI Board of Management.

Etta, who joined the Authority at the beginning of September, was previously a solicitor in general practice and has experience in dealing with medical negligence cases.

Etta succeeds Heather Simmonds who became Director of the Authority at the beginning of May following the retirement of David Massam.

The Authority looks forward to the valuable contribution to its work which it believes Etta will make.

Substantiation

There has recently been criticism in New Scientist about the failure of companies to provide substantiation for claims when requested to do so. Companies are reminded that Clause 7.4 of the Code states that "Substantiation for any information, claim or comparison must be provided without delay at the request of members of the health professions or appropriate administrative staff. It need not be provided, however, in relation to the validity of indications approved in the marketing authorization".

If a company is unable, or is not prepared, to provide substantiation for a particular claim, then it cannot make that claim. It cannot make a claim and then later plead that the information required to substantiate it is confidential.

Gifts and inducements

In July, the Medicines Control Agency issued a cautionary letter to companies warning them about the provision of gifts in relation to the sale of medicines, pointing out that this was not permitted by the Advertising Regulations.

The Code of Practice prohibits the use of gifts as inducements to purchase by Clause 18.1 and three companies have been ruled in breach of it for that reason. The supplementary information to Clause 18.1 will be changed in the 1998 Code in order to make the position absolutely clear. It is not permissible to offer mountain bicycles, gift vouchers and the like in relation to the sale of medicines, even if they are presented as alternatives to financial discounts.

Gifts to medical and pharmaceutical advisors

It has recently been suggested to the Authority that Clause 18.1 of the Code does not prohibit the offer of gifts, benefits in kind or pecuniary advantages to medical and pharmaceutical advisors because that clause forbids them as an inducement to prescribe, supply, administer or buy any medicine, and medical and pharmaceutical advisors do none of those things.

It may well be that a strict interpretation of Clause 18.1 allows that conclusion and the wording will be examined when the Code is next reviewed. In the meantime, companies are advised not to provide any gifts etc to advisors other than those permitted by Clause 18.2. Any attempt to influence advisors by means of gifts and the like would be regarded as bringing the industry into disrepute, contrary to Clause 2 of the Code, or, at the very least, as failing to meet high standards, in breach of Clause 9.1.

Details of the changes to the Code

The following are the principal changes for the 1998 edition:

- The exclusion from the Code given in Clause 1.2 for replies to individual enquirers, including letters in professional journals, will not apply unless the reply is accurate and does not mislead.
- Clause 2 relating to bringing discredit upon the industry is widened so that it applies to "activities or materials associated with promotion" rather than simply methods of promotion.
- The supplementary information to Clause 3.1 relating to advance notification of new products or product changes has been revised in the light of experience.
- Clause 8.2 relating to the disparagement of the opinions of health professionals now makes it clear that the health professions themselves must not be disparaged.
- Supplementary information has been added to Clause 9.9 relating to the declaration of sponsorship to say that the declaration must be sufficiently prominent to ensure that readers are aware of it at the outset.
- The supplementary information for Clause 11.1 relating to the supply of unsolicited reprints now applies to "providing" rather than "sending" so as to cover supply by representatives.
- Clause 14.1 relating to certification now makes it clear that a registered medical practitioner must be one of those to certify - current use of the word "doctor" has been wrongly interpreted on occasion - and also allows for a dentist to certify instead of a medical practitioner in the case of a product for dental use only.
- Clause 16.2 relating to examinations for representatives has been changed, as has its supplementary information, in order to clarify the position as to the calculation of the two years which is allowed before a representative must have passed one of the ABPI's representatives' examinations.
- The supplementary information to Clause 18.1 has been revised in relation to terms of trade to make it clear that personal benefits, such as gift vouchers, cannot be given in relation to the promotion of medicines, even if they are presented as alternatives to financial discounts; the exclusion from the Code of certain trade practices given in Clause 1.2 has been similarly amended.

Full details of the changes have been sent to pharmaceutical companies and to advertising and public relations agencies on the Authority's mailing lists.

Provision of medical and educational goods and services

At the suggestion of the Code of Practice Appeal Board and with the support of the ABPI Board of Management, the Authority has established a Working Party to review the provision of medical and educational goods and services by pharmaceutical companies in relation to the current requirements of the Code of Practice. A number of recent cases have exposed uncertainties in this area.

The Working Party is chaired by Mr Mike Gatenby, General Manager of Zeneca Pharma.

Proposed changes to the Advertising Regulations

In August, the Medicines Control Agency circulated proposals for amending The Medicines (Advertising) Regulations and The Medicines (Monitoring of Advertising) Regulations. In a covering letter to the Authority, the Agency stated that it proposed to address current areas of misunderstanding by strengthening the Regulations. The Agency believed that it was crucially important to the effectiveness of the self-regulation system to eliminate misunderstanding.

The Authority has some concerns about the proposals and both the Authority and the ABPI have submitted comments to the Medicines Control Agency.

The Internet

The September/October edition of MAIL from the Medicines Control Agency states that the Code of Practice for the Pharmaceutical Industry is being revised to explicitly state that it covers the Internet.

That is not actually so, but the Code does cover the Internet. Clause 1.2 makes it clear that it covers any promotional activity, including use of electronic media.

The Authority issued advice on the Internet and the Code in the May 1996 edition of the Code of Practice Review and copies of that advice are available on request. It is the Authority's intention to issue further guidance on the matter in due course.

Security of samples

Following a death as a result of taking products which appear to have been misappropriated from a representative's stock of samples, a Coroner has written to the Authority about security. The Coroner's letter is reproduced below and companies are asked to review their own security procedures. Companies are reminded that Clause 17.9 of the Code states that "Companies must have an adequate system of control and accountability for samples which they distribute".

The Coroner writes:

"I am now writing pursuant to Rule 43 of the Coroners Rules 1984 to report to you certain matters which I consider to be of public concern and which you may feel should prompt you to either issue further guidelines to the pharmaceutical industry or

remind them of existing guidelines. The facts which have come to light are as follows:

1. That samples of prescription only drugs have been delivered to a sales representative by couriers in a manner whereby any member of the sales representative's household could sign for the drugs and therefore have access to them.
2. That drugs have been stored by a sales representative in his car and garage in circumstances where other members of his family could have access to them, i.e. stored insecurely.
3. That in respect of the particular circumstances, there was and is no system for auditing stocks of drugs in the possession of the sales representative to control them and reveal samples going missing.
4. That out of date samples have not been returned by the sales representative to his company for destruction but have been disposed of by flushing down the toilet into the public water system.

Whilst the company in question was aware of the ABPI Code of Practice requirements, it is clear that in this case those requirements were not operated in such a way that prevented the problems which I have catalogued above. You may feel that at the very least, pharmaceutical companies should be reminded of the necessity to police their operation of the Code by their employees."

A happy event

Emer Flynn, who has been away on maternity leave since July, now has a baby son, Cormac. The Authority sends its best wishes to Emer and her family.

During Emer's absence, Vicki Meyrick has taken over Emer's responsibilities, including the organisation of seminars on the Code of Practice.

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:

Thursday, 22 January 1998
Tuesday, 10 February 1998
Wednesday, 11 March 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.

CASE AUTH/514/3/97

NO BREACH OF THE CODE

DIRECTOR/MEDIA v ZENECA

Support of out-of-hours centre

An article in Pulse headed "GP defends drug company backing" was taken up as a complaint under the Code. The article said that Zeneca was providing £30,000 over three years to support an out-of-hours centre and had also provided training in information technology.

The Panel considered that the support was in accordance with the supplementary information to Clause 18.1 which allowed the provision of medical and educational goods and services if this was done in such a way as not to be an inducement to prescribe, supply, administer or buy any medicine. The support did not result in any personal benefit to the doctors concerned and was not tied to the use of Zeneca's products. There was nothing to say that the training in information technology had been done inappropriately. No breach of the Code was ruled.

As with all cases, a report was subsequently received by the Code of Practice Appeal Board. The Appeal Board expressed concern that the Panel might have made its ruling on incomplete information and referred the matter back to the Panel. The Panel obtained further information from Zeneca and again came to the conclusion that there had been no breach of the Code.

COMPLAINT

An article in Pulse, 22 February 1997, was taken up as a complaint under the Code with the Director acting as the complainant in accordance with the usual practice. The article was headed "GP defends drug company backing" and indicated that Zeneca was giving £30,000 spread over three years to support an out-of-hours centre based at the East Cheshire Trust in Macclesfield. The company employed more than 5,000 staff in the area and regarded the donation as a good investment in the community.

One of the general practitioners involved with the centre was quoted as saying "Drug companies have moved on from buying GPs dinner or a scraper for their windscreen". "I can't see any difference between this and discounting vaccines. I can understand some GPs feeling uneasy about all the changes taking place but I want to be positive about the new opportunities". Zeneca had also helped to train information technology (IT) staff at the GP's seven handed practice but the company's involvement had no strings attached. The general practitioner said that "We don't even use Zeneca emergency drugs".

In writing to the company attention was drawn to the requirements of Clause 18.

RESPONSE

Zeneca Pharma said that wherever Zeneca operated in the world, it aimed to support relevant initiatives which benefited sick or underprivileged groups. Zeneca Pharmaceuticals' international headquarters and manufacturing facility was based in the Macclesfield area in Cheshire and employed over 5,500 staff. In addition to supporting numerous national and international initiatives, Zeneca also provided support in the local community. Zeneca Pharmaceuticals won a Queen's Award for Export Achievement in 1995 and, in recognition, the business made donations to the David Lewis Centre for Epilepsy and to the mental health charity SANE. The contribution by the business enabled the first UK Saneline centre outside London to be established in Macclesfield and Zeneca's support funded volunteer recruitment and training. Zeneca had also provided continuing support for the East Cheshire Hospice (in Macclesfield) and donated £15,000 last year bringing total support to the Hospice since its foundation to £160,000. These were only isolated examples of Zeneca's support in the local community. Another example of support was the Macclesfield and Chelford Primary Care Centre, the subject of the Pulse article.

In April 1996, Zeneca Pharmaceuticals committed itself to providing £30,000 over three years to help establish an out-of-hours GP facility for the residents of Macclesfield and Chelford. This facility was the first of its kind in Cheshire and served as an emergency night centre staffed by local GPs with nursing support. The doctor quoted in the article was a partner in one of the local group practices which benefited from this facility. It should be emphasised that the Macclesfield and Chelford Primary Care Centre benefited all the practices in the area which it served and also, of course, the local residents who now had access to an out-of-hours centre. It was regrettable that the Pulse article, by choice of the title "GP defends drug company backing", implied some kind of wrongdoing which needed to be defended and gave the false impression that it was only one particular doctor or his practice which had received benefit.

As far as Zeneca was able to establish, the reference in the Pulse article to Zeneca helping to train IT staff at the GP's practice related to an event which took place more than three years ago. At that time, some members of the group practice support staff attended an IT training course at the local college of further education. By coincidence, the tutor was a Zeneca employee. When the local medical representative heard of this, Zeneca believed that she arranged with the tutor for a continuation of the training to be provided "on-site" at the group practice as a goodwill gesture. Zeneca had no reason to believe there was any other motive behind this arrangement. Zeneca regretted that it was unable to provide more precise details but the representative left the company's employment two and a half years ago and, as a consequence, it had been difficult to establish all the facts of the case so long after the event.

In conclusion, Zeneca emphasised that its support for the Macclesfield and Chelford Primary Care Centre was part of the general support which the company provided for the local community in which it and its employees resided and this support was not in any way associated with the sale or promotion of the company's products. Zeneca believed the activity of the local medical representative in

facilitating IT training at a group practice was a gesture of goodwill and there had been no suggestion that it was linked in any way to promotional activity. Zeneca believed that its activities in relation to both matters were and had been wholly consistent with the requirements of Clause 18 of the Code.

The following further points were made by Zeneca in response to questions put by the Authority.

(i) The Primary Care Centre was based in part of the Macclesfield District General Hospital. The building in which the Primary Care Centre was situated was owned by the East Cheshire NHS Trust and the facilities were rented on an annual basis.

(ii) Zeneca Pharmaceuticals was committed to providing £30,000 over three years. The first £10,000 of the donation had already been paid and this money was spent largely on equipment and start-up costs. The remainder of the £30,000 was being used as a contribution towards running, maintenance and nursing support costs. The overall costs of the Primary Care Centre were well in excess of the contribution being made by Zeneca. For example, the cost of the nursing support alone was currently £35,000 per year.

(iii) None of the doctors or staff at the centre enjoyed personal financial gain as a result of Zeneca's contribution to the centre and, since the premises were rented, there were no privately owned disposable assets to be realised on retirement of any of the participating doctors.

PANEL RULING

The Panel noted that the contribution to the costs of the Macclesfield and Cheshire Primary Care Centre was part of Zeneca's support for local facilities. The contribution did not result in any personal benefit to the doctors concerned and was not tied to the use of Zeneca's products. The Panel considered that the contribution was in accordance with the supplementary information to Clause 18.1 of the Code, relating to gifts and inducements, which did not did not prevent the provision of medical and educational goods and services which would enhance patient care or benefit the National Health Service. The provision of such goods or services must not be done in such a way as to be an inducement to prescribe, supply, administer or buy any medicine. No breach of the Code was ruled.

In relation to the provision of training in information technology, the Panel did not consider that this was unacceptable and there was nothing to say that it had been done inappropriately. No breach of the Code was ruled.

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The report for the case had subsequently been considered by the Code of Practice Appeal Board as usual. The Appeal Board was concerned that the Panel might have made its ruling on incomplete information. The concern related to the potential personal financial gain to doctors or staff at the out-of-hours centre. Zeneca had been specifically asked whether any of the doctors using the centre would benefit personally from Zeneca's sponsorship, either currently or when they retired and took their share of practice assets etc. The reply from Zeneca had been that none of the doctors or staff at the centre would enjoy personal financial gain as a result of Zeneca's contribution to the centre. Since the premises were rented there were no privately owned disposable assets to be realised on the retirement of any of the participating doctors.

The Appeal Board had considered that Zeneca should provide further information to support the submission that none of the doctors or staff at the centre enjoyed personal financial gain as a result of Zeneca's contribution to the centre. It was assumed that funding for the out-of-hours centre came from each participating practice. The view was expressed that if Zeneca had not sponsored the facility for the sum of £30,000, then the money would have had to come from the doctors themselves. The Appeal Board considered that the doctors would benefit indirectly if their contribution to the centre would be less due to the Zeneca sponsorship.

The Appeal Board requested that the matter be pursued by the Authority. Further information was then obtained from Zeneca.

FURTHER RESPONSE

Zeneca explained that the Macclesfield and Chelford Primary Care Centre which was based at the Orthopaedic Department at Macclesfield District General Hospital was operated by a non profit making cooperative of 37 general practitioners providing an out-of-hours medical service for 72,000 patients in the area.

The basis on which the facility was set up was neither to purchase nor alter premises but to rent existing premises already equipped to provide medical services. This explained why the centre operated out of the Orthopaedic Department of the local hospital.

Zeneca had ascertained that the cooperative did purchase a computer and a fax machine. An auriscope was donated by another pharmaceutical company. The disposable assets of the cooperative were clearly negligible and the question of a doctor retrieving his share on retirement or leaving the area did not really arise.

Zeneca said that funding of the facility was to be principally by government grant with some financial contribution from each of the participating general practitioners. The co-operative applied for a grant but the award fell short of the requested level. Consequently the cooperative sought sponsorship to make up the shortfall. At this point Zeneca Pharma (the UK business company) was approached with a request to be the sole sponsor, Zeneca being the major employer in the area. Another local (non-pharmaceutical) business had already offered sponsorship in the event of Zeneca not providing the required funding. The company emphasised that the cooperative approached Zeneca and at no time did Zeneca seek to be involved in the setting up of, or operation of, the out-of-hours centre. Zeneca believed this was an important community project worthy of support. Zeneca Pharma consulted other business units of Zeneca to raise the necessary fundings. Zeneca offered £30,000 in sponsorship. Had Zeneca not offered this sum, the company had no doubt that other sponsorship would have been available to the cooperative. What level of funding this would have been and what effect it might or

might not have had on the level of contributions from the doctors would never be known. In the light of the above information Zeneca was pleased to contribute to the funding of the out-of-hours facility for the benefit of the citizens of the area where its business was based. Zeneca regarded this as an ethical and responsible activity demonstrative of good citizenship.

The question of whether or not it would have been necessary for the GPs to provide additional personal funding had Zeneca not provided sponsorship would remain unanswered. However the company regarded the question as somewhat academic. Clause 18.1 of the Code stated that no gift, benefit in kind or pecuniary advantage should be offered or given to members of the health profession .... as an inducement to prescribe, supply, administer or buy any medicine. The supplementary information to Clause 18.1 stated that Clause 18.1 did not prevent the provision of medical goods and service which would enhance patient care or benefit the National Health Service. The provision of such goods or services must not be done in such a way as to be an inducement to prescribe, supply, administer or buy any medicine.

There had never been any suggestion that Zeneca's sponsorship of this out-of-hours centre, which clearly enhanced patient care, had been linked to promotion of its medicines or to an inducement to prescribe, supply, administer or buy its medicines. Zeneca did not manufacture medicines which were normally associated with an out-of-hours emergency GP service. Indeed in the original article in Pulse, the doctor concerned was quoted as saying "We don't even use Zeneca emergency drugs". The company noted that the Appeal Board had not raised any questions on this aspect and therefore assumed that the Appeal Board and the Code of Practice Panel were satisfied on this point.

Zeneca concluded that it believed its sponsorship of the out-of-hours centre was a legitimate and ethical activity and as it was not linked to any promotional activity for any of Zeneca's products the company failed to see how it could be in breach of the Code.

PANEL RULING

The Panel noted that the Appeal Board was not empowered to re-open cases that had been decided by the Panel and which were not the subject of an appeal. If, however, a decision of the Panel had been based on incomplete or erroneous information, it was possible for the matter to be re-opened and for the Panel to make a fresh decision. This had been the advice of the Chairman which had been accepted by the Code of Practice Appeal Board when it had considered the report for the case in question.

Turning to the matter now before it, the Panel noted that the case had arisen as a result of an article published in Pulse. The Director was acting as the complainant. There was no external complainant and there had been no appeal.

The Panel considered that this was a difficult case. Zeneca had provided sponsorship for an out-of-hours centre in an area where its business was based. Zeneca employees and others would benefit from the out-of-hours centre. It was a local initiative. It was not unusual for pharmaceutical companies to support their local community. The support in this instance was not for general community activities, such as sponsorship of a local football team or items for a local school, but was direct support for local doctors.

The Panel noted that if Zeneca had not provided the sponsorship it was likely that a non-pharmaceutical local business would have provided the sponsorship. The alternative would have been for the GPs to have increased their own financial contribution to the out-of-hours centre. The Panel noted that the GPs had received a government grant but it had fallen short of the requested level.

The Panel examined Clause 18.1 of the Code and its supplementary information. The supplementary information stated that Clause 18.1 did not prevent the provision of medical and educational goods and services which would enhance patient care or benefit the National Health Service. The provision of such goods and services must not be done in such a way as to be an inducement to prescribe, supply, administer or buy any medicine. By providing money to the out-of-hours centre, patient care might be enhanced, but the GPs could be said to benefit personally from the sponsorship in that the GPs did not have to increase their own financial contributions to the centre. Under the Code the only gifts that could be given to healthcare professionals in relation to the promotion of medicines were those supplied in accordance with Clause 18.2 of the Code. Such gifts had to cost the company no more than £5 and had to be relevant to the practice of the recipient's profession or employment.

The Panel accepted that there was no direct inducement for the doctors to prescribe, supply, administer or buy any medicine linked to the offer of sponsorship. The cooperative had approached Zeneca for sponsorship. Zeneca representatives were not involved. There would inevitably be a spin off in that Zeneca would be viewed in a positive manner by the doctors concerned. The Panel noted that the Code referred to gifts, benefits in kind or pecuniary advantages being offered or given as an inducement to prescribe, supply, administer or buy any medicine. The Medicines (Advertising) Regulations 1994 stated that "... where relevant medicinal products are being promoted to persons qualified to prescribe or supply relevant medicinal products, no person shall supply offer or promise to such persons any gift, pecuniary advantage or benefit in kind, unless it is inexpensive and relevant to the practice of medicine or pharmacy".

The Panel considered that the sponsorship of the out-of-hours centre was sufficiently removed from promotion. The transaction as a whole was non promotional. It had been a corporate activity. If representatives had been involved it would have been more questionable. It was a local initiative and would benefit the local population.

Given the circumstances the Panel ruled no breach of Clause 18.1 of the Code.

Proceedings commenced **6 March 1997**

Case completed **24 July 1997**

CASE AUTH/517/3/97

HEALTH AUTHORITY v BRISTOL-MYERS SQUIBB

PACE Project

Two health authority personnel complained about the way in which Bristol-Myers Squibb had implemented an agreement that it would provide the use of an echocardiography (echo) machine in their area, which was one of the pilot sites for the Kings Fund Promoting Action on Clinical Effectiveness (PACE) Project. The complainants alleged that use had been made of the provision of the service by Bristol-Myers Squibb to promote its ACE inhibitor, Staril.

The Panel accepted in principle that the provision of an open-access echocardiography programme by a pharmaceutical company was acceptable as it would enhance patient care and benefit the NHS. The question was whether the arrangements for the service constituted an inducement to prescribe, supply, administer or buy any medicine.

The Panel noted that the representatives' information clearly linked the service with the promotion of Staril and stated, for example, that it aimed to "... drive sales of Staril." In the Panel's view, the material for representatives instructing them about the project clearly associated the echo service with the promotion of Staril. The company had not made sufficient effort to clearly differentiate the provision of the echo service from the prescribing of Staril and had given the impression that the two were linked. Overall the Panel considered that the project amounted to an inducement to prescribe Staril in breach of the Code. A breach of Clause 2 was also ruled. Upon appeal by Bristol-Myers Squibb, the Panel's rulings were confirmed. The Appeal Board considered that despite the merits of the echo service, the way in which it had been delivered was in breach of the Code.

A Health Authority's consultant in public health and its pharmaceutical adviser jointly complained about Bristol-Myers Squibb Pharmaceuticals Limited. The complainants explained that their Health Authority was one of 16 national pilot sites for the Kings Fund Promoting Action on Clinical Effectiveness (PACE) Project which in its district was focusing on encouraging better diagnosis and management of heart failure. Part of the project involved encouraging provider trusts to set up open access echocardiography (echo) services but there was a delay with the main local hospital in being able to implement this service. As part of its discussions with all pharmaceutical companies providing ACE inhibitors, the Health Authority explored the possibility of Bristol-Myers Squibb providing a mobile machine for the district. The Health Authority had the money for the technician support and whenever the Health Authority worked with pharmaceutical companies a written agreement was drawn up to clarify the responsibilities of each party. A copy of the agreement was provided.

COMPLAINT

On 22 January 1997 the Health Authority had its first clinical meeting following the agreement about the use of the mobile echo machine. Bristol-Myers Squibb asked for a slot in that meeting for it to give a clinical presentation using videos of echoes to demonstrate the use of the technique and for a company representative to describe the mobile echo project that Bristol-Myers Squibb was running.

The complainants referred to the third section of the agreement drawn up between Bristol-Myers Squibb and the Health Authority. The final paragraph in that section stated that "BMS representatives may visit practices and hospitals in their normal way, however, they should not use their support of the PACE project to gain access to clinicians or to imply any preferential treatment". The complainants were therefore extremely distressed to hear that the representative at the meeting stated that, because Bristol-Myers Squibb was providing the echo machine, representatives would be visiting practices in three weeks time to determine the workload for that machine. The representative also stated that unless three in every nine ACE inhibitor prescriptions were for the Bristol-Myers Squibb product, fosinopril (Staril), then the company would cease to provide the machine. The complainants were reviewing whether they wished to try to continue such an agreement with the company. The complainants wrote to local GPs following this meeting expressing their concern over the tactics used. At that time the complainants believed that this was an isolated occurrence and were prepared to believe that this was a misunderstanding of some sort. However, two practices had since contacted the complainants to describe similar behaviour from Bristol-Myers Squibb representatives. Copies of the two letters were provided.

The GPs who had written the letters both described an audit procedure which Bristol-Myers Squibb carried out in order to identify patients who might benefit from echocardiography. One of the GPs specifically asked whether there was any catch to this service and was told definitely not. Following completion of the audit one GP wrote that "It became clear at this stage that Squibb were asking for us to put any patient who went forward for echo and who were found to have CCF requiring an ACE inhibitor on to their brand product" and "I ..... was surprised to hear that Squibb were indicating that they would need three out of nine patients ..... to go on their brand product to pay for the service". The other GP wrote that a Bristol-Myers Squibb employee ".... made it clear in no uncertain terms that I was being expected by the company to prescribe Staril in return for the service which had been provided, and that no more echo sessions would be booked until this happened. When I protested ... said that they would be happy if 50% of the patients started on ACEs were given Staril".

The complainants alleged that the behaviour of Bristol-Myers Squibb contravened Clauses 2 and 18.1 of the Code.

RESPONSE

Bristol-Myers Squibb divided its response into four parts as follows:

1 Background to the Bristol-Myers Squibb mobile echo programme

Bristol-Myers Squibb said that there was wide agreement amongst UK cardiologists that patients with congestive heart failure (CHF) were both under-diagnosed, and under-treated. There was inappropriate use of loop diuretics and under-use of ACE inhibitors which had been shown to significantly prolong survival in these patients. The definitive proof of CHF was by Doppler-assisted echocardiography (echo). Although there was recognition of the need for echo to improve diagnosis of CHF, health authorities were not yet able to provide open access echo to GPs in all parts of the country. To meet this need, a number of companies had initiated projects which provided open access echo to GPs who considered that their patients would benefit.

A pilot programme was launched by Bristol-Myers Squibb in October 1994 for approximately six months. During this period the British Cardiac Society (BCS) and the British Society of Echocardiography (BSE) raised a number of questions concerning the equipment, documentation and experience of the operators. A full review of the service was undertaken and following extensive discussions the programme was developed in line with the requirements of the BCS and the BSE. The new programme was launched in June 1996. All operators were BSE accredited as requested by the BCS and BSE. Payment of the operator was from Bristol-Myers Squibb, the GP practice, the health authority or a combination of these. Extensive documentation supporting the programme was provided.

Bristol-Myers Squibb said that the programme was launched to a small specialist field force at a two day training course in early 1996, which included training on heart failure, introduction to the documentation, familiarisation with the equipment and a demonstration of the echo machine in use from a consultant cardiologist. The Code of Practice issues relating to the provision of this type of service were also covered, including the fact that the provision of these services could not be used as an access item, and nor could business be negotiated or exchanged in return for the provision of the service. The representatives' training manual was provided.

Between June and December 1996 over 250 echo clinics took place. To date in 1997, over 50 clinics had been held. The service was highly valued by both GPs and health authorities. In two areas the programme had been implemented in conjunction with the health authority which was paying the operator's fees.

2 PACE meeting on 22 January 1997

Bristol-Myers Squibb had interviewed separately the two senior sales personnel who were involved in the meeting. A memo was received describing the meeting from a third representative who was present.

a) Background to the meeting

Bristol-Myers Squibb said that its health care business manager held discussions with the Health Authority's consultant in public health, who was seeking support for the PACE project. When she described the Bristol-Myers Squibb echo project the consultant considered that it would be ideal. At a subsequent meeting in December, the consultant agreed with Bristol-Myers Squibb on the sites, the length of the pilot and the funding. Bristol-Myers Squibb's project leader for PACE in the area was at this meeting. At the meeting it was decided where the two sites for the echo machine were to be. It was agreed at the meeting that the pilot phase of the programme would run for six months from January to June 1996 and that it would then be reviewed, and this was reflected in the written agreement between the company and the Health Authority.

It was also agreed at this meeting to hold a launch meeting at which the echo programme would be demonstrated to local GPs and cardiologists; it was agreed that Bristol-Myers Squibb would invite three local consultant cardiologists. The launch meeting was organised by a local representative for Bristol-Myers Squibb who drew up an agenda which had been agreed with the Health Authority's consultant and asked for a slot at which Bristol-Myers Squibb could present the echo programme.

b) Description of the meeting

Bristol-Myers Squibb said that when its staff arrived at this meeting they noticed that several other companies were present with promotional stands and mentioned to the Health Authority that since this was a PGEA (Postgraduate Education Allowance) sponsored meeting there should not be any promotion of products. No action was taken by the Health Authority in response to this comment.

Following presentations from two cardiologists and the Health Authority's consultant, and as agreed with the latter, Bristol-Myers Squibb's primary care executive gave a presentation on the Bristol-Myers Squibb echocardiography service. This presentation was not promotional. She gave a general background to the Bristol-Myers Squibb echo programme and mentioned that demand for the use of echo machines consistently exceeded supply and that a lot of time had been wasted with inappropriate referrals. She gave guidance on the type of patient who should be referred so as to focus the audience on patients who would benefit from the service. She mentioned that there had been discussions with the BCS and the BSE and that the programme only used accredited technicians. The company had made a large investment and the commitment for the national programme was for a period of two years. At the end of her presentation she stated that the service would be provided in the area for an initial period of six months as agreed with the Health Authority, and would then be reviewed. The Health Authority's consultant asked the audience whether they wanted the service. The doctors all gave vocal assent that they wished to have the service and a general discussion ensued.

During this open discussion the primary care executive mentioned that the echo machines were in high demand and that Bristol-Myers Squibb would need an estimate of the number of patients who would be referred. The doctors did not know how many patients might be referred, and she then informed them that sessions would run in the early evening so that the doctors running the echo machines could do this after their working day. There would be 6-8 patients per session and, as Bristol-Myers Squibb had responsibility for administering the

diaries for the echo machine, she asked if it would be helpful if representatives called on practices to determine the numbers who might be referred. She suggested that this could take place in the two weeks following the meeting. A GP replied that three weeks would be a better period. There was agreement by the GPs present that a representative would call to speak to the practice manager to organise the logistics of the access to the echocardiography machines.

Bristol-Myers Squibb said that its primary care executive mentioned that the company had two ACE inhibitors, Capoten and Staril, as the latter was missing from the Health Authority consultant's slide. A GP asked "What is Staril?". A cardiologist gave a précis of the compound.

A GP then said "It would be unfair if we used your equipment and did not prescribe Staril".

Another GP said "What have we got to do? How will you measure sales?"

She replied "By RSA sales".

The second GP: "Come on, what will you be looking for?"

She replied: "We know that we will get the return on investment if we get three out of nine patients put on Staril but it would be different in ..... because ..... are paying the technicians".

Bristol-Myers Squibb said that its primary care executive, other representatives present at the meeting, and one of the cardiologists present, all specifically denied that she had said, as stated in the complaint, "Unless three in every nine ACE inhibitor prescriptions were for the Bristol-Myers Squibb drug, Staril, then Bristol-Myers Squibb will cease to provide the machine". This was a misinterpretation of what occurred. Bristol-Myers Squibb said that at no time did its executive link the number of prescriptions to the provision of the service. She was replying to quite difficult questions by a GP who appeared to have a specific interest in the business return of the project to Bristol-Myers Squibb.

Bristol-Myers Squibb said that the offer by the representative to visit the practices who were to be provided with the echo machine was purely as an administrative support to the project; this support was considered appropriate and agreed to by all the GPs present at the meeting. The consultant cardiologist who participated at the meeting made it clear that the service would be open to all general practices. Bristol-Myers Squibb refuted the suggestion that the company used its support of the PACE project to gain access to clinicians or to imply any preferential treatment. The discussion about access to practice managers was purely in relation to the administration of the echo programme. Since the company was delivering the echo machines and was in charge of the diary for the sessions, representatives had to administer the programme and had been asked to do so by the Health Authority. Part of this administration was the booking of patients which had been delegated to the local Bristol-Myers Squibb representative, and who therefore had to find out how many patients would be referred.

3 Training of the involved representatives

Bristol-Myers Squibb confirmed that all the representatives involved had either passed the ABPI examination or were exempt by virtue of their number of years' experience. In addition its primary care executive had received two days of specific training on the echo programme and when being interviewed about this complaint demonstrated (unprompted) awareness of the particular issues relating to Clause 18.1 of the Code.

4 Complaints from general practitioners in response to the letter from the health authority

Bristol-Myers Squibb noted that the Health Authority wrote to all GPs in the area and had forwarded two letters to the Code of Practice Authority. Bristol-Myers Squibb had not seen the letters although relevant passages of the letters had been provided to the company by the Code of Practice Authority. Bristol-Myers Squibb noted that the Health Authority had solicited these complaints from amongst a large number of GPs, and they had selected two letters from amongst what might have been a greater number of replies. In addition the primary care executive who was administering the echocardiography project and the local representative both specifically denied saying to any GPs involved with the project, that the service in the area would be withdrawn if they did not prescribe Staril. Bristol-Myers Squibb said that this was simply not the way the representatives had been trained to administer the programme and was not the way they currently did so. The representatives described two surgeries in the area where echo had been implemented but Staril had not been prescribed following the sessions. The company continued to provide echo to these surgeries. Bristol-Myers Squibb said that the area sales manager responsible for the area had discussed with his team how careful they would have to be when implementing the programme with respect to the Code. The instruction had always been to sell Staril first before the echo programme was mentioned, and at no time were representatives to suggest or imply that the use of the machines was dependent upon prescription of Staril. Bristol-Myers Squibb attached letters from two other GPs, testifying to the ethical way in which the service was provided and the benefits their patients received from it.

PANEL RULING

The Panel noted that the supplementary information to Clause 18.1 of the Code stated "Clause 18.1 does not prevent the provision of medical and educational goods and services which will enhance patient care or benefit the National Health Service. The provision of such goods or services must not be done in such a way as to be an inducement to prescribe, supply, administer or buy any medicine. They must not bear the name of any medicine but may bear a corporate name." In the Panel's view companies wishing to take advantage of the supplementary information must clearly separate the offer of such goods and services from any promotional activity. This would include any past or promised support of the company. The Panel noted, however, that where services were provided by pharmaceutical company representatives it would be difficult to separate the service from the promotional activities of the representatives.

The Panel considered that in principle the provision of an open access echo programme by a pharmaceutical

company would enhance patient care and benefit the NHS. The question for the Panel was whether or not the arrangements for the service in question constituted an inducement to prescribe, supply, administer or buy any medicine.

The Panel noted that the administrative support for the service was provided by representatives.

The Panel reviewed the support documentation provided by Bristol-Myers Squibb and noted that the leaflet entitled "Information for representatives" (ref: STA - E/004) began with the question "What is the BMS mobile echocardiography service?" to which the first sentence of the answer was "This service is a pioneering, educational initiative that aims to enhance the level of cardiac care available in the community and drive sales of STARIL". In addition the leaflet stated that "The scale of this project underpins the commitment that BMS has to the future, and especially to STARIL" and that the echo service would "Help meet sales targets with opportunities to sell the whole spectrum of BMS products". The representatives' manual stated that "This service is limited to a few practices who have supported the work of Bristol-Myers Squibb in the past". In addition the manual stated that in order to achieve an acceptable return on investment representatives should aim for 5 echo sessions per week, 40 per year; 9 patients echoed per session with 3 patients identified and initiated on an ACE-inhibitor per session. In a section instructing representatives on how to organise each echo session representatives were told to arrange preliminary practice meetings. It was suggested that at these meetings a cardiologist would discuss echocardiography and its importance, cardiovascular issues and appropriate treatment and explain the rationale for Staril as an ACE inhibitor of choice. The manual also encouraged representatives to be present at each echo session, with the agreement of the other parties concerned, and to arrange a ten minute "de-brief" at the end to check that the session went well and assess the prescriptions or potential prescriptions generated. Representatives were told that one aim was to ensure that practices understood that they were expected to prescribe an ACE inhibitor where appropriate.

In the Panel's view the material for representatives instructing them about the project clearly associated the echo service with the promotion of Staril. Having Bristol-Myers Squibb representatives so closely involved with a service designed to improve the diagnosis of congestive heart failure and encourage a greater use of ACE inhibitors would effectively promote Staril. The arrangements were such that the project fell within the supplementary information to Clause 18.1 of the Code. Overall the Panel considered that the project amounted to an inducement to prescribe Staril. The Panel therefore ruled a breach of Clause 18.1.

The Panel noted that the complainants had alleged that the Bristol-Myers Squibb representative had linked the prescription of Staril to the provision of the echo service. The Panel noted that the representative had said in her presentation on 22 January that the service was to be reviewed after the initial six months and in the general discussion which followed and under direct questioning, that to get a return on investment three out of nine patients would have to be put on Staril. While the two statements were not explicitly linked by the representative, the Panel did not consider it unreasonable for some of the audience to connect the two and assume that without the return on investment Bristol-Myers Squibb might withdraw the service after the first six months. In the Panel's view the company had not made sufficient effort to clearly differentiate the provision of the echo service from the prescription of Staril and had given the impression that the two were linked. A breach of Clause 2 was ruled.

During its consideration of this case the Panel noted that there was a pharmacy monitoring scheme whereby Bristol-Myers Squibb would be able to collect data on prescriptions written after each echo session. The pharmacist was asked to complete a form which required the pharmacist's name and address and details about the prescription. A professional fee of £3 in the form of Marks & Spencer's vouchers was to be paid. The representatives were instructed to remove the echo pharmacy envelope if no ACE inhibitor was recommended. It appeared to the Panel that data would only be collected when an ACE inhibitor had been prescribed. In the Panel's view this was too selective. If the scheme was to provide a comprehensive picture of the impact of the echo service on prescribing habits then data regarding all prescriptions should have been collected and analysed. In addition the professional fee paid to the pharmacist for providing the data in the form of Marks & Spencer's vouchers was inappropriate as a professional payment. The Panel requested that its views on these matters be passed on to Bristol-Myers Squibb.

APPEAL BY BRISTOL-MYERS SQUIBB

Bristol-Myers Squibb addressed Clauses 18.1 and 2 in turn.

Clause 18.1

Bristol-Myers Squibb noted that the supplementary information to Clause 18.1 stated that this clause "... does not prevent the provision of medical and educational goods and services which will enhance patient care or benefit the National Health Service".

Bristol-Myers Squibb said that its mobile echo programme was first launched in 1994 and had been reviewed by both the British Cardiac Society and the British Society of Echocardiography (BSE). All operators involved in the programme were BSE accredited to ensure that the programme was run to the highest clinical standards.

Despite widespread recognition of the value of echocardiography in the diagnosis and management of congestive heart failure (CHF), this service was not yet widely available to general practitioners. Although GPs managed the majority of CHF patients, many health authorities had been unable to provide an open access echocardiography service to assist GPs in their management of CHF patients. Thus the mobile echo programme enhanced patient care and benefited the NHS.

Bristol-Myers Squibb also noted that the supplementary information to Clause 18.1 stated that "The provision of such goods and services must not be done in such a way as to be an inducement to prescribe supply, administer or buy any medicine". Bristol-Myers Squibb said that at no

time had the provision of the mobile echo programme been conditional upon any commitment or undertaking to prescribe, administer or supply any of its medicines.

Based on its knowledge of echocardiography services and the heart failure market, Bristol-Myers Squibb had predicted that for every nine patients echoed, three patients would be identified as requiring an ACE inhibitor. Bristol-Myers Squibb had calculated that if this prediction was correct then the echo programme would be affordable to the company as well as valuable to patients. This prediction was also communicated, not inappropriately, to the specialised team of representatives administering the echo programme. There was a clear distinction between predicting what the effects of implementing a service might be and making the provision of a service conditional on prescribing a medicine.

There was strong evidence that the mobile echo programme was established and run in such a way that it could not be mistaken for, and was not perceived as, an inducement to prescribe.

Bristol-Myers Squibb drew attention to the following points:

- In correspondence from two GPs, which was typical of the response the company had received from physicians in connection with the mobile echo programme, the programme was described as "helping to develop a cardiology service of the future" and providing "significant health gains" and more importantly as "well run and organised".
- In two areas, the programme had been implemented in conjunction with local health authorities which had expressed no concerns whatsoever regarding the way in which the service was administered.
- The representative who was the subject of this complaint was a member of a specialised team specifically trained on the mobile echo programme itself together with the legal and ethical restraints on the provision of such a service. In particular, representatives had been instructed to ensure that they never inadvertently suggested or implied that placement of the programme was dependent upon prescribing.
- It was entirely reasonable that Bristol-Myers Squibb wished to review the provision of the service after six months; this was common practice in areas where the programme had been implemented since all parties involved were keen to review the impact of the service on patient management and utilisation of joint resources.
- The Panel had considered it inappropriate for representatives to be involved in the provision of this type of service. However, the Code of Practice did not preclude the involvement of pharmaceutical company representatives in the provision of medical services. Many pharmaceutical companies appropriately employed their representatives in an administrative capacity in the implementation of such services. Representatives were the largest proportion of the work force of any pharmaceutical company; to implement a medical service without involving representatives would incur prohibitive costs. The resultant loss of services would be detrimental to patients and the NHS.

Bristol-Myers Squibb said that there was also strong evidence to refute the allegation that at the meeting, arranged by the Health Authority to introduce GPs to echocardiography and the programme, a Bristol-Myers Squibb representative made a presentation which suggested the mobile echo programme would be used as an inducement to prescribe:

- The Bristol-Myers Squibb representative did not link provision of the programme to prescribing. A consultant cardiologist present at the meeting had commented that, at the meeting, the representative "faced aggressive and direct questioning from the audience" but "at no time did she link this (the prescribing of fosinopril) to the provision of the service". This was acknowledged by the Panel which stated "the two statements were not explicitly linked by the representative". However the Panel considered that some members of the audience might have connected the two. In fact, the only members of the audience to have made this connection were two representatives of the Health Authority. Bristol-Myers Squibb noted that the Health Authority did not raise its apparent concerns either at the meeting or subsequently with the company but that its letter of complaint to the Code of Practice Authority was written more than six weeks after the meeting.

There was therefore no contemporaneous evidence to support the allegation.

- With regard to the suggestion that representatives should call on practice managers 2-3 weeks later to determine the possible level of uptake of the programme and deal with administrative matters; this was made by one of the GPs in the audience. There was no suggestion, or intention, that these visits would be used to gain 'preferential treatment'. The representatives' training manual clearly defined the representatives' role at such visits as purely administrative.

Bristol-Myers Squibb also noted that the supplementary information to Clause 18.1 stated that any service "... must not bear the name of any medicine but may bear a corporate name". The mobile echo programme did not bear the name of, and was not associated with, any particular medicine but did carry corporate identity.

Bristol-Myers Squibb did not accept that the provision of the mobile echo programme had breached Clause 18.1 of the Code.

Clause 2

Bristol-Myers Squibb noted that Clause 2 required that "Methods of promotion must never be such as to bring discredit upon, or reduce confidence in, the pharmaceutical industry".

There was no evidence that Bristol-Myers Squibb had made the provision of the mobile echo programme conditional upon the prescription of its medicines.

Bristol-Myers Squibb maintained that through the training of experienced, specialised representatives it had clearly differentiated between the provision of the mobile

echo programme and prescription of its medicines.

The fact that several health authorities, including that involved in the complaint, as well as many consultant cardiologists and GPs wished to continue their association with the programme and Bristol-Myers Squibb, despite the allegations made against the company, indicated that the company and the programme were highly regarded. Bristol-Myers Squibb had behaved in an ethical and responsible manner both in the implementation of the mobile echo programme and in the investigation of the complaint. The company did not accept that it had brought discredit upon, or reduced confidence in, the pharmaceutical industry and therefore did not consider that the ruling of a breach of Clause 2 was justified.

In summary, Bristol-Myers Squibb refuted the allegations since they were not corroborated by the evidence of either Bristol-Myers Squibb or independent attendees at the meeting or by the company's past experience of providing this service.

The company pointed out that the pharmacy monitoring scheme criticised by the Panel had been discontinued. It was also pointed out that in the area involved all practices were jointly invited by the Health Authority and the company to attend the meeting to find out more about the echo service.

APPEAL BOARD RULING

The Appeal Board noted that partnership schemes were legitimate activities for a pharmaceutical company to undertake provided that such schemes were in accordance with the Code. The pharmaceutical industry was becoming more involved with sponsorship etc of the NHS. It was a growing area. Each scheme would have to be considered on its merits.

The Appeal Board considered that in principle the provision of an open access echocardiography service by a pharmaceutical company would enhance patient care and benefit the NHS. The Appeal Board noted that the echocardiography service provided by Bristol-Myers Squibb was a high quality service delivered by trained accredited personnel. The service had to be provided in such a way as to not be an inducement to prescribe, supply, administer or buy any medicine.

The Appeal Board noted that the supporting documentation directed at the Bristol-Myers Squibb representatives was highly motivational and made it clear that their involvement with the echo service would be an opportunity for them to increase the sales of Staril. The representatives' manual stated that personal success in the service would be measured by prescriptions. The manual encouraged representatives to play an active role in the echo session which meant that they might be in a position to influence the final prescribing decision. The manual stated that if the GP prescribed at the echo session this was "more convenient for the patient and allowed more representative influence over the prescription".

The Appeal Board noted that the material provided to health professionals contained references to Staril. The echo summary data form for the practice, which was to be completed after each session, contained columns headed "Staril/ACE Recommended Y/N" and "Staril/ACE Initiated Y/N". Doctors were also provided with leaflets headed "The Ageing Heart: Your Questions Answered" which they could give to patients and which explained about heart failure and its treatment. These leaflets, however, were product specific and stated that they were for patients prescribed Staril.

The Appeal Board considered that the very close involvement of Bristol-Myers Squibb personnel with the service and the references to Staril in the support documentation would effectively promote Staril. In the Appeal Board's view prescribers would be under pressure to prescribe Staril. The Appeal Board considered that the provision of the service was not dependent on the prescription of Staril but that the service amounted to an inducement to prescribe Staril.

The Appeal Board considered that the provision of the echo service had been actively used by Bristol-Myers Squibb as a promotional opportunity for Staril. Representatives had been encouraged to view the service as such. There had been little or no differentiation between the provision of the service and the promotional activities of the representatives. The Appeal Board considered that despite the merits of the echo service the way it had been delivered was in breach of the Code. The Appeal Board upheld the Panel's rulings of breaches of Clause 18.1 and Clause 2.

The appeal therefore failed.

During its consideration of this case the Appeal Board was concerned about a patient support scheme which was described in the representatives' manual and referred to "a free enrolment gift". Obviously any items provided to patients by the company needed to comply with the Code and the Appeal Board asked that the company be reminded of this.

Complaint received **14 March 1997**

Case completed **8 August 1997**

CASES AUTH/525/4/97 & AUTH/526/4/97

MERCK SHARP & DOHME v PARKE-DAVIS AND PFIZER

Promotion of Lipitor

Merck Sharp & Dohme complained about the promotion of Lipitor (atorvastatin). Lipitor was jointly promoted by Parke-Davis and Pfizer and the matter was taken up with both companies.

The claim "The most effective cholesterol lowering agent" was ruled to be in breach of the Code because a superlative could be used only in relation to a simple statement of fact that could be clearly demonstrated. The Panel did not consider that the claim met that criterion as the matter was far from simple. The claim was not one of a clearly provable fact but was one which was not indisputable. It was in breach of the Code whether or not it could be substantiated.

The use of landmark studies relating to the benefits of cholesterol reductions were ruled not to breach the Code. The Panel did not consider it unreasonable to refer to the benefits of reducing cholesterol levels shown in various studies. It was made clear that none of the studies had used atorvastatin. Upon appeal by Merck Sharp & Dohme, the Appeal Board confirmed the Panel's ruling of no breach.

A claim "Strength.....never before seen in statin therapy" was taken by the Panel in company with the statements "Range...to treat more profiles than any other statin" and "Simplicity - never before seen in therapy" and ruled not to be in breach. The Panel accepted that Lipitor was licensed to treat a broader range of indications than the other statins. Upon appeal by Merck Sharp & Dohme in relation to the first of these statements, the Appeal Board considered that there was data to support it and upheld the Panel's ruling of no breach. Panel rulings that there had been no breach in relation to the claims "Lipitor lowers cholesterol to a significantly greater extent than other statins currently available" and "Strength - to reduce cholesterol and triglyceride levels more than any other statin" were similarly upheld by the Appeal Board.

A claim "Simplicity - to bring 70 - 90% patients to their EAS treatment goals with a 10mg once daily starting dose" was ruled by the Panel not to be in breach. Having noted the methodological reasons for the choice of studies upon which the claim was based and for the exclusion of another, and the effect on the figures of including that other, the Panel considered that it was not misleading to refer to 70 - 90%.

Merck Sharp & Dohme Limited complained about the promotion of Lipitor (atorvastatin) by Parke Davis & Co Limited and Pfizer Limited. Lipitor was jointly promoted by Parke-Davis and Pfizer. Parke-Davis responded on behalf of both companies.

A LIPITOR MAILING (Z590/90026A)

1 Claim: "The most effective cholesterol lowering agent"

COMPLAINT

Merck Sharp & Dohme alleged that this claim was in breach of Clauses 7.2, 7.3 and 7.8 of the Code as it was all-embracing, used a superlative which was misleading, was inaccurate and could not be substantiated. In order to make such a claim there would have to be clinical data directly comparing atorvastatin with all other cholesterol lowering products. Despite repeated requests, Merck Sharp & Dohme had not been shown any data from studies which directly compared simvastatin (its product Zocor) and atorvastatin. It had been offered the opportunity to see unpublished data which Parke-Davis believed supported the claim. However, in order to do so, it would have to sign a confidentiality agreement and it was quite clear that the data was not freely available. Accordingly it could not be relied upon to support promotional claims until such time as it became freely available to those who asked to see it in accordance with Clause 7.1 of the Code. Such data that had been presented had been inadequate to support the claim.

Treatment of patients with cholesterol lowering products had been revolutionised with landmark studies such as 4S (simvastatin) WOSCOPS/CARE (pravastatin); the primary goal of treatment was no longer simple cholesterol reduction but was now to improve the prospects of the survival of patients with cardiac risk factors, such as angina or having had a heart attack. Parke-Davis was aware of this fact and also aware that there was no data demonstrating any such improvement in the prospects of survival of patients treated with atorvastatin. The company's data was limited to showing simply the extent to which atorvastatin lowered cholesterol and not whether this had a direct impact on patients' survival prospects. Accordingly Parke-Davis had avoided clearly and unequivocally restricting its promotional statements to cholesterol lowering in the hope that the reader would ascribe to atorvastatin the benefits that had been clinically proven (in statistically significant terms) only in relation to simvastatin.

The claim misled because it failed to recognise the crucial importance to any cholesterol agent of reducing morbidity and mortality. Lipitor had no data on these important endpoints and failure to recognise this misled the reader.

Merck Sharp & Dohme said that Parke-Davis had attempted to compare the claim with one made by Merck Sharp & Dohme in a Zocor promotional piece in 1994, "... Zocor is unsurpassed as monotherapy in lowering plasma cholesterol" Merck Sharp & Dohme made two points in relation to this. Firstly it was accurate and suitably restricted in its scope and thus provided an excellent contrast with the more sweeping claim complained of here. In addition, as outlined above, the treatment of patients with cholesterol lowering medicines had been revolutionised since the publication of the 4S study and the real measure of effectiveness in such a treatment was now seen as its effect on coronary and other mortality. Thus simply stating "The most effective cholesterol lowering agent" without making it clear that the claim was restricted to simple reductions in plasma cholesterol would mislead readers into believing that atorvastatin

had a proven effect on mortality, which it did not.

Use of landmark studies in the detail aid (Z579/90015)

Merck Sharp & Dohme said that a letter to it from Parke-Davis dated 27 March 1997 stated that that company had been "....extremely careful not to make any claims beyond Lipitor's proven ability to lower cholesterol and triglycerides more effectively than any other pharmacological lipid modulating agent". Merck Sharp & Dohme found this surprising as the second and third pages of the detail aid were devoted to studies which had demonstrated a number of benefits of cholesterol reduction which had not been demonstrated with atorvastatin. Clearly the reader was intended to extrapolate those benefits to atorvastatin which was grossly misleading. Given the comments of Parke-Davis in its letter, Merck Sharp & Dohme found it odd that reference to any benefit of treatment beyond simple cholesterol reduction appeared in the detail aid.

RESPONSE

Parke-Davis submitted that it was claiming that Lipitor was superior at lowering cholesterol and it had substantial information to support the claim. The company accepted that the claim included a superlative but it firmly believed that it could be fully substantiated and therefore was not in breach of the Code. The claim related to Lipitor in the context of other cholesterol lowering agents. In a recent review article (Farmer and Gotto 1996) it was reported that the other statins currently available reduced LDL-cholesterol by 20 - 40% throughout their currently approved dosage range. Bile acid sequestrates reduced LDL-cholesterol by 15 - 30%, nicotinic acid reduced LDL-cholesterol by 10 - 25% and fibrates typically reduced LDL-cholesterol by 10 - 15%.

With regard to Merck Sharp & Dohme's allegations that the claim was misleading because it failed to recognise the crucial importance to any cholesterol lowering agent of reducing morbidity and mortality and failed to recognise that no such endpoint data were available for Lipitor, Parke-Davis disagreed for two reasons. Firstly, the claim was a simple statement of fact and only referred to cholesterol lowering. Secondly it was recognised that blood cholesterol levels in hypercholesterolaemic patients were a surrogate for cardiovascular risk. This was widely accepted and it was nonsensical to suggest that references to cholesterol reduction without mention of reducing morbidity and mortality were misleading.

With regard to cholesterol lowering, lovastatin was not extensively discussed except where relevant as the product was not available in the UK. Since simvastatin and pravastatin were the leading agents in the UK and both were well known to be more efficacious than fluvastatin, this particular agent had not been discussed either.

With regard to Lipitor's comparative performance in lowering cholesterol, a dose ranging study by Nawrocki (1995) demonstrated that atorvastatin (10-80mg) in hypercholesterolaemic patients significantly reduced LDL-cholesterol by 41% to 61% compared with an 8% increase in the placebo treatment group ($p<0.05$). Similar dose dependent reductions from baseline in total cholesterol were also seen and ranged from 30% in the 10mg atorvastatin group to 46% in the 80mg atorvastatin treatment group compared with a 5% increase in the placebo treatment group ($p<0.05$).

Similar results were obtained in patients with mixed hyperlipidaemia (Gmerek 1996). Efficacy analysis showed mean changes in LDL-cholesterol of -37%, -42%, -50% and - 59% at 10, 20, 40 and 80mg atorvastatin daily ($p<0.05$).

Parke-Davis submitted that the magnitude of change demonstrated in these studies was supportive of its efficacy claims. In addition it had substantial data from double blind, randomised comparative studies. In these direct comparisons, atorvastatin lowered cholesterol more than either pravastatin or simvastatin.

A study by Egros (1996) was a one year, double blind, parallel group study in which 305 patients with LDL-cholesterol ≥4.1mmol/l were randomised to receive either 10mg atorvastatin or 20mg pravastatin. At week 16 the dose of each statin could be doubled if any patient's LDL-cholesterol was still above the treatment goal of 3.4mmol/l. After 16 weeks of treatment, atorvastatin 10mg and pravastatin 20mg daily reduced LDL-cholesterol by 35% and 24% ($p<0.05$) respectively. These changes in lipid levels were maintained at one year (LDL-cholesterol reduced by 35% with atorvastatin compared with 23% pravastatin ($p<0.05$)).

In a second one year double blind parallel group study by Wagner (1996), 297 patients with LDL-cholesterol between 4.1 and 6.5mmol/l were randomised to receive either atorvastatin 10 or 20mg (n=224) or pravastatin 20 or 40mg daily (n=73) based on their baseline LDL-cholesterol levels and their cardiovascular risk which was assessed according to the European Atherosclerosis Society (EAS) guidelines. At weeks 8 and 16 the dose of each statin could be increased if any patient's LDL-cholesterol was still above the EAS guideline goal. Atorvastatin was significantly more effective in lowering LDL-cholesterol than pravastatin (39% vs 29%, $p<0.0001$). Atorvastatin was also significantly more effective in lowering apoB (25% vs 20%, $p<0.05$) and triglycerides (13% vs 8%, $p<0.05$).

A study by Bracs (1996) compared atorvastatin 10mg daily with simvastatin 10mg daily in a 52 week, double blind, parallel group study in 192 patients with LDL-cholesterol ≥4.1mmol/l. The dose of each statin was doubled at week 16 if any patient's LDL-cholesterol was still above the treatment goal of 3.4mmol/l. After 16 weeks, atorvastatin and simvastatin reduced LDL-cholesterol levels by 37% and 30% respectively ($p<0.05$). At the end of the study the mean percentage decrease in LDL-cholesterol from baseline was 38% for atorvastatin compared to 33% for simvastatin ($p<0.0036$). Similarly atorvastatin was significantly better than simvastatin in reducing total cholesterol, triglycerides, VLDL-cholesterol and apolipoprotein B.

Parke-Davis submitted that the data substantiated the claim and clearly reflected all the evidence in a fair manner.

Parke-Davis said that Merck Sharp & Dohme had been provided with the above information upon which it relied as substantiating the claims made. It was in substance the same data as that made available to the Medicines Control

Agency (MCA). Nevertheless knowing that further relevant data would shortly be published, this fact was made known to the MCA (although it had indicated that the existing data was sufficient to substantiate the claims). Similarly Parke-Davis had thought it right, when it met with Merck Sharp & Dohme in March, to share the provisional, incomplete experimental data available at that stage on this further, direct head to head comparison of atorvastatin with all doses of simvastatin. It was clearly stated to Merck Sharp & Dohme at that meeting and in writing on subsequent occasions that Parke-Davis was not relying on these data to support any of the claims and, further, it was not cited or referenced in the promotional materials. The data was from an in-house research report that had not been finalised. Merck Sharp & Dohme acknowledged that it treated such preliminary data in a similar fashion. Parke-Davis explained that the data was confidential while awaiting acceptance for publication and it was Merck Sharp & Dohme which originally suggested that a secrecy agreement might be a way forward for disclosure of further information. Parke-Davis agreed this might be a possibility and had asked the company to formally request the data under such an agreement for onward consideration by headquarters staff. No such request was received.

Use of landmark studies in the detail aid

Parke-Davis responded to allegations concerning reference in the detail aid to landmark studies which had demonstrated that various cholesterol lowering agents, including statins, had beneficial effects on certain coronary risk factors and upon survival, on the basis that by doing so the company had misled doctors into believing that atorvastatin would have similar beneficial effects.

Parke-Davis submitted that it was justified to refer to the available data provided it was made clear that atorvastatin was not used in these landmark studies. It had not suggested in the detail aid, and had never suggested, that atorvastatin had been studied in any major end point study. The company had been extremely careful not to make a claim that specific study data existed other than in respect of Lipitor's superior ability to lower cholesterol and triglycerides. However, it submitted that it was appropriate to refer physicians to the mass of epidemiological and experimental evidence demonstrating the benefits of lowering cholesterol in hypercholesterolaemic patients as a way of "setting the scene" to put the relevance of atorvastatin's cholesterol lowering effect into clinical context.

Atorvastatin lowered total cholesterol, LDL-cholesterol and triglycerides and raised HDL-cholesterol. This was expressly set out in the materials and the data was adequate to support the claims. There was a wealth of epidemiological and experimental data referring to different intervention therapies involving diet, surgery, resins, fibrates and statins using different methodologies and conducted in different centres but all reaching the same overall conclusions. The data put beyond doubt that a reduction in the concentration of non HDL-cholesterol in blood by any intervention (be it diet, surgery or medicines) led in general terms to a reduction in heart disease. This was the basis on which the licensing authority would have initially authorised cholesterol lowering therapies and the basis on which Lipitor was granted its licence. In other words it was accepted that cholesterol lowering might be used as a marker for reducing heart disease risk.

Parke-Davis submitted that use of markers was common in medicine and there were many instances where assessment of a marker or surrogate was used to provide an indication of disease or disease risk. For example, reduced bone density as a marker for osteoporosis and high blood pressure as a marker for heart disease or haemorrhagic stroke. Merck Sharp & Dohme was of the view that it was acceptable shortly after simvastatin was launched and prior to the cardioprotective indication being granted, to make the claim "reducing cholesterol to help prevent coronary heart disease".

Parke-Davis said that it was scientifically sound to attribute the benefits shown in the landmark studies such as 4S, WOSCOPS and CARE to the ability of HMG CoA reductase inhibitors in general to modulate the lipid profiles of patients with existing or pre-existing coronary heart disease. There was no data to suggest this was not the case or that the benefit should be attributed to some other unique property of these particularly studied statins. Accordingly it could not be an unrealistic assumption that atorvastatin, by virtue of its competitive inhibition of HMG CoA reductase (the identical mechanism of action of all other statins) and consequent effect on blood lipids, would also reduce heart disease.

Such an extrapolation was not only reasonable but was scientific and supported by the vast majority of medical opinion. The fact that doctors regarded the beneficial effects of statins as being attributable to the class was borne out by a recent survey conducted in the USA by Merrill Lynch where it was reported that physicians regarded the benefits demonstrated in the statin landmark studies as being benefits which could be attributed to the class as opposed to benefits unique to a single product. This was the opinion of a lead investigator in the simvastatin 4S study. Moreover the fact that statins as a class were regarded as producing cardiovascular benefits was evidenced by such references as the British National Formulary which stated that there was evidence that statins produced important reductions in coronary events, in all cardiovascular events and in total mortality in patients aged up to 70 years, with coronary heart disease and with plasma cholesterol of 5.5 - 8mmol/l.

Once a class effect had been properly established it became unethical and wasteful of both resource and lives to repeat identical placebo control trials. In Parke-Davis' view it was simply not reasonable to deny or delay the benefit of all innovative advances from medicine unless each and every landmark trial was repeated. This was of course the potential flaw in an over rigid application of the evidence based medicine theoretical approach which at some point in a therapeutic area had to accept that medical practice had moved to a new knowledge base upon which a new generation of innovative products could build.

In preparing the detail aid, Parke-Davis had referred to previous guidance issued by the Authority and the Appeal Board on the use of clinical studies in promotional material where the studies in question had not been conducted with precisely the product which was the

subject of promotion. In Case AUTH/364/10/95 the Panel noted that it was not unacceptable in principle to use data from studies not carried out on the product being promoted, provided that the presentation was not misleading. In that particular case the company concerned had similarly referred to a landmark study, but had not specifically referred to the original agent used in the landmark study. Page 2 of Parke-Davis' detail aid identified each agent used in the studies by generic name and it was therefore very apparent to the reader that none of the studies related to atorvastatin. Of course doctors would be well aware that a new compound in this well known class of products was unlikely to have been the subject of long term studies of this nature, but the company had put the issue beyond doubt. Doctors would also be aware of the precise statin molecules used in the 4S and WOSCOPS studies because of the enormous scientific and promotional impact these landmark studies had had with this audience. The company submitted it was perfectly legitimate to use the information on pages 2 and 3 to "set the scene" and put the importance and relevance of atorvastatin's cholesterol lowering effect in context.

The content of the detail aid was set out in sufficiently clear terms so as not to mislead doctors. Parke-Davis did not believe reference to the landmark studies and the importance of blood cholesterol would render the detail aid in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel examined the data provided to support the claim "The most effective cholesterol lowering agent". It noted the data in the review by Farmer, whereby the statins, fluvastatin (10 to 40mg per day), lovastatin (10 to 80mg per day), pravastatin (10 to 40mg per day) and simvastatin (5 to 40mg per day) decreased LDL-cholesterol by 20 - 40%, the bile acid sequestrants, cholestyramine and colestipol, reduced LDL-cholesterol by 15 - 30%, nicotinic acid reduced LDL-cholesterol by 10 - 25% and the fibrates, gemifibrozil and clofibrate, reduced LDL-cholesterol by 10 - 15%.

The Panel noted that the placebo studies showed that atorvastatin reduced LDL-cholesterol by 41 - 61% at 10 to 80mg and total cholesterol from 30 - 46% at 10 to 80mg in hypercholesterolaemic patients. In mixed hyperlipidaemia efficacy analysis showed LDL-cholesterol changes of -37% to -59% at 10mg to 80mg.

The Panel then examined the comparative data. All three studies, Egros, Wagner and Bracs, used the starting dose of 10mg atorvastatin with the potential to increase the dose if necessary. The Bracs study compared 132 patients receiving atorvastatin with 45 patients receiving simvastatin. The Egros study compared 227 patients receiving atorvastatin and 78 patients receiving pravastatin. The Wagner study compared 224 patients receiving atorvastatin and 73 receiving pravastatin. All three studies showed that atorvastatin lowered cholesterol more than either pravastatin or simvastatin.

The Panel noted that Parke-Davis did not have direct head to head comparisons of atorvastatin with every product available for cholesterol lowering. It noted that the review article indicated that statins lowered LDL-cholesterol by 40%. Studies with atorvastatin and placebo had shown reductions in LDL-cholesterol of 37% to 59% at various doses. The comparative data gave LDL-cholesterol lowering figures for atorvastatin 10mg of 35% (Egros) and 38% (Bracs). The Wagner study showed a reduction of LDL-cholesterol of 39% at a mean dose of 29mg atorvastatin. The Panel noted that the comparative data was provided in the form of abstracts.

The Panel was concerned that the claim used the superlative "most". The supplementary information to Clause 7.8 of the Code stated that the use of a superlative which could be substantiated was a simple statement of fact which could be very clearly demonstrated, such as that a particular medicine was the most widely prescribed in the UK for a certain condition, if this was not presented in a way which misled as to its significance. The Panel considered that in this instance the use of the superlative "most" did not meet the criterion as being in relation to a simple statement of fact as, in the Panel's view, the matter was far from simple. The Panel considered that it was not acceptable to use a superlative in the present context. The claim was not one of a clearly provable fact but was one which was not indisputable. The Panel ruled a breach of Clause 7.8 of the Code. The use of the word "most" in the claim was in breach of the Code whether or not the claim using it could be substantiated. It was not therefore necessary to consider the alleged breach of Clause 7.3.

The company had data to support the claim and that data had been sent to Merck Sharp & Dohme. The Panel did not accept that the claim would mislead readers into believing that atorvastatin had a proven effect on mortality. In the Panel's view the claim was not for a therapeutic advantage but for a reduction in cholesterol levels. No breach of Clause 7.2 of the Code was ruled.

The Panel noted that Clause 7.1 of the Code only required that a company should make information available. In the Panel's view this meant that companies were obliged to provide general information such as that which a health professional enquiring about a product might expect. Companies were not obliged under Clause 7.1 to provide every piece of information requested. In the Panel's view Parke-Davis had supplied information as required by Clause 7.1 and no breach of the Code was ruled. The company had supplied Merck Sharp & Dohme with the studies referred to in its response. Parke-Davis had not provided Merck Sharp & Dohme with the additional confidential data. This had not been referenced in the promotional materials. There was however no allegation regarding Clause 7.4.

Use of landmark studies in the detail aid

The Panel examined the detail aid. Page 2 highlighted the benefits of reducing cholesterol levels giving details of the various studies and the agents used in each study. Page 3 referred to the need for greater efficacy. The Panel did not accept that it was unreasonable for the detail aid to refer to benefits of reducing cholesterol levels in various studies. It was made clear that none of the studies used atorvastatin. The Panel did not accept that the detail aid was misleading in this regard.

The Panel did not accept that because Lipitor had no data on the end points of reducing morbidity and mortality, the failure to recognise this in the claim misled the reader.

No breach of Clause 7.2 of the Code was ruled. This was appealed by Merck Sharp & Dohme.

APPEAL BY MERCK SHARP & DOHME

Use of landmark studies in the detail aid

Merck Sharp & Dohme said that the second page of the detail aid was devoted to the studies which had demonstrated cardiovascular morbidity and mortality benefits with other cholesterol-reducing agents. These studies had been included in the detail aid in conjunction to the claims of superiority in an attempt to imply that atorvastatin would have superior effects on atheroma progression, CV events, CV mortality and total mortality.

Merck Sharp & Dohme believed this to be in breach of Clause 7.2 of the Code since the reader was obviously intended to extrapolate these benefits to atorvastatin. This was confirmed by the response of Parke-Davis to Merck Sharp & Dohme's complaint which stated, "... a class effect had been properly established" and "it could not be an unrealistic assumption that atorvastatin... would also reduce heart disease". This revealed that a major tenet of the promotional campaign of Parke-Davis was to promote the idea that the available clinical outcomes data were simply the reflection of a common effect of all lipid-lowering agents, especially the clinical outcome data relating to Zocor, the only statin proven to reduce coronary and total mortality. Not only was this clinically simplistic, given the wide variety of patient profiles, drugs and treatment regimes in the various studies, but the generalisation of the data also completely lacked credibility because of the inclusion of the Helsinki Heart Study involving gemfibrozil. In the detail aid, this study was included to support the claim that simple cholesterol reduction "Reduced CV events". However, despite the ability of gemfibrozil, seen in the study, to effectively lower LDL-cholesterol there was a (non-significant) increase in total mortality seen in the study! This was at odds with the results of the 4S study (which "reduced total mortality") and clearly demonstrated the danger of attempting to generalise the unique results of individual studies.

The results of the Helsinki Heart Study, for example, served to demonstrate that until the long-term use of atorvastatin had been rigorously studied, it could not be 'assumed' that the levels of cholesterol reduction seen with atorvastatin would translate into other clinical benefits.

The reduction of cardiovascular morbidity and mortality seen with Zocor, and the reduction of cardiovascular events seen with other lipid-lowering agents, might be due to factors other than the lowering of LDL-cholesterol, such as plaque stabilisation or endothelial function. Jackson (1997), and Vaughan *et al* (1996), demonstrated that it was not the opinion of the vast majority of the medical profession that all statins had the same effects. Generalisations of data from major outcomes trials set a precedent against evidence based medicine, which had become a cornerstone of contemporary clinical practice.

It was curious that a survey carried out in the US by Merrill Lynch, a company of investment analysts, should be quoted as an authoritative measure of clinical opinion.

Also, it should be noted that whilst Parke-Davis stated "This was the opinion of a lead investigator in the simvastatin 4S study", Merck Sharp & Dohme was not aware of the 4S investigator publishing this view and would be interested to see more details of this.

Parke-Davis had stated that "Once a class effect had been properly established it became unethical ... to repeat placebo-controlled trials". This however was not Merck Sharp & Dohme's challenge. Now that therapy with Zocor had been accepted as the gold standard in treating post-MI and angina patients with elevated cholesterol, future studies could be expected aimed at establishing clinical outcomes to compare newer products with Zocor, rather than placebo. This would clearly not be unethical. For the reasons stated above, Merck Sharp & Dohme believed that until such trials had taken place and the results published, the sweeping generalisations implied in the table on page 2 of the detail aid were in breach of Clause 7.2.

RESPONSE FROM PARKE-DAVIS

Parke Davis said that the initial complaint under this heading was that by referring to the landmark studies which demonstrated that various cholesterol lowering agents, including statins, had beneficial effects on cardiovascular risk factors and upon survival, Parke-Davis was misleading doctors into believing that Lipitor would have similar beneficial effects. It was Parke-Davis' position that the current scientific consensus against which its promotion must be judged was that statins as a class did have beneficial effects upon cardiovascular risk factors and survival arising out of their cholesterol lowering effects. Parke-Davis believed this position was substantiable, properly supported by the available evidence, and was accepted by the Panel. On appeal, Merck Sharp & Dohme had stated that the inclusion of the landmark studies implied that Lipitor would have superior effects on atheroma progression, cardiovascular events and mortality, and total mortality.

i) Class effect of statins Parke-Davis reiterated that it did not suggest in the detail aid, and had never suggested, that Lipitor had been investigated in any major end point study, or indeed that its effect in terms of cardiovascular morbidity or mortality were superior to other statins. Parke-Davis nevertheless still firmly believed that it was appropriate to refer physicians to the mass of epidemiological and experimental evidence demonstrating the benefit of lowering cholesterol.

These data had put beyond reasonable doubt that a reduction in the concentration of non-HDL-cholesterol in blood by any intervention (including statins) led in general terms to a reduction in heart disease. This was the basis upon which the licensing authority would have initially authorised cholesterol lowering therapies and the basis upon which Lipitor was granted its licence. Indeed, a recent meta-analysis by Gould *et al* sponsored by Merck Sharp & Dohme concluded that cholesterol lowering conferred an overall benefit as shown by the reductions in coronary heart disease (CHD) and total mortality, and suggested that the magnitude of benefit was related to the degree of cholesterol lowering achieved.

There would be clinicians who did not agree with a particular consensus but it would be hard to imagine a

substantial difference within the class when three chemically distinct agents in the same class - simvastatin, pravastatin and now fluvastatin - had already demonstrated broadly similar clinical benefit to each other in differing populations of hypercholesterolaemic patients. No-one doubted that lowering raised blood pressure with antihypertensive drug therapy was of clinical benefit in reducing cardiovascular risk; however, diuretics and beta-blockers were the only two agents for which long-term effects on morbidity and mortality had been demonstrated. Likewise, it was now widely accepted that statins as a class were regarded as producing cardiovascular benefits. The British National Formulary (Number 33; March 1997) stated: "There is evidence that statins produce important reductions in coronary events, in all cardiovascular events, and in total mortality in patients aged up to 70 years with coronary heart disease and with plasma cholesterol of 5.5 - 8 mmol/litre". This was "evidence based medicine" being applied appropriately to a class of drug in actual clinical practice and the suggestion by Merck Sharp & Dohme that this was an inappropriate generalisation was not supportable.

Parke-Davis pointed out that Merck Sharp & Dohme had stated that it was clinically simplistic to promote the idea that the clinical outcomes data were a reflection of the common effect of lipid lowering therapies. When a physician decided to use a lipid lowering agent such as Lipitor to lower cholesterol, (s)he did so consistent with current scientific and medical opinion that cholesterol lowering was a marker for reducing the risk of cardiovascular disease. Parke-Davis did not believe that this was unreasonable. The physician would be basing his or her decision to prescribe on the scientific merit of the data from all sources. It would in fact be simplistic to base prescribing on a single study such as 4S (which itself only examined a specific hypercholesterolaemic patient subgroup) rather than viewing this study in the context of the substantial and expanding knowledge base of different patient groups and therapies.

ii) Use of the Helsinki Heart Study Parke-Davis stated that Merck Sharp & Dohme noted that all cause mortality was not reduced in the Helsinki Heart Study but Parke-Davis would disagree with Merck Sharp & Dohme's contention that it could not be cited in support of the position that cholesterol reduction reduced CV events. It was an important milestone in the evolution of the cholesterol story, demonstrating that lowering cholesterol in a primary prevention setting reduced cardiovascular death. The results for all cause mortality (referred to by Merck Sharp & Dohme as "total mortality"), were not the same as the results reported in 4S but Parke-Davis did not believe that Merck Sharp & Dohme were interpreting the difference correctly when saying the results were "at odds with" 4S. Scientifically, the studies independently evaluated different classes of compound in different patient populations and the average total reduction in cholesterol with gemfibrozil in the Helsinki Heart Study was 11% compared to 25% with simvastatin in 4S. Further, the Helsinki Heart Study was not powered to study gemfibrozil's effect on all cause mortality, whereas the 4S study was. The point was that the Helsinki Heart Study was appropriately cited as one of 11 studies which all demonstrated a benefit from reducing cholesterol.

iii) Other effects of statins Parke-Davis pointed out that Merck Sharp & Dohme contended that the reduction in cardiovascular morbidity and mortality seen with simvastatin and other lipid lowering agents might be due to factors other than lowering LDL-cholesterol and it cited two articles which it alleged supported the premise that not all statins had the same effect.

The scientific point that Jackson and Vaughan were making was that there might be other factors in addition to LDL-cholesterol lowering that contributed to these proven clinical advantages. There was absolutely no suggestion that clinical benefit might be conferred by these other factors instead of LDL-cholesterol lowering. However, the important point here was that there was no proof or evidence that these supposed effects were in any way unique or exclusive to simvastatin and pravastatin. These additional effects were as likely to be properties common to this class as the better documented effect that statins had on cholesterol itself.

iv) Use of Merrill Lynch data The survey conducted in the USA by Merrill Lynch reported that physicians regarded the benefits demonstrated in the statin landmark studies as being benefits which could be attributed to the class, as opposed to benefits unique to a single product. These clinicians' interpretation was likely to be based on the historical data as well as the statin landmark trials. Merck Sharp & Dohme stated that it was "curious" that this market research data from a company of investment analysts should be quoted without making any specific allegation or complaint for Parke-Davis to respond to. This was valid market research and was provided to and accepted by the Panel for its consideration. The opinion of the 4S investigator cited by Parke-Davis in its letter to the Panel further supported Parke-Davis' position and was in the form of a personal communication to its medical director.

v) Comparative outcomes data Whether or not simvastatin could be claimed to be the "gold standard" was not at issue here. The fact was that cholesterol lowering had been shown to improve clinical outcome by virtue of reduction in cardiovascular mortality and morbidity and overall mortality. Whilst there might be scope for comparative outcomes studies, Parke-Davis believed that the case for a clinical benefit with cholesterol lowering was beyond dispute. Further, it believed that its outcomes research should be focused in other areas of clinical importance where research had not yet demonstrated clinical benefit. Parke-Davis was currently undertaking such endpoint studies comparing Lipitor with placebo in non-insulin dependent diabetes mellitus patients as well as comparing Lipitor with placebo in cerebrovascular disease and acute coronary syndrome. In addition, Parke-Davis firmly believed the current absence of a Lipitor outcomes study did not, and should not, prevent it from describing the cholesterol lowering benefits of its product in the proper clinical context. Parke-Davis would reiterate that it had not sought to promote Lipitor as better than simvastatin with regard to clinical outcome, and that its promotional positioning had been greater cholesterol lowering efficacy and the ability of a substantial number of patients who were treated with Lipitor to achieve European Atherosclerosis Society target cholesterol levels, assessed according to their risk for CHD. Parke-Davis noted that Merck Sharp & Dohme had

accepted the Panel's ruling with regard to efficacy in this context.

FURTHER COMMENTS FROM MERCK SHARP & DOHME

Merck Sharp & Dohme said that it remained its contention that the reference to landmark studies in the detail aid was a breach of Clause 7.2 of the Code because the way in which they were presented would lead the reader to assume that the "benefits" referred to were class effects of statins and one could therefore assume that therapy with atorvastatin would give at least similar benefits.

i) Class effects of statins While Merck Sharp & Dohme accepted that there was no direct claim that atorvastatin had been studied in any major end point study, nor could such a claim be made, it did believe that such landmark studies were referred to in the detail aid in order that the reader would assume that the outcomes seen in these studies would also be seen in patients treated with atorvastatin.

Merck Sharp & Dohme accepted that clinical evidence indicated that certain cardiovascular benefits had been associated with treatment with various cholesterol-lowering agents. It further agreed that it was safe to draw some very broad generalisations from these studies; it was clearly for those who wished to make such generalisations to support them before the Authority. Merck Sharp & Dohme did not, however, believe that it was either safe or responsible to promote the idea that each clinical benefit which had been seen in each study could automatically be deemed to be a class effect, common to all statins. This was particularly true in the case of "reduced total mortality". Various studies had been undertaken which were powered to demonstrate a reduction in total mortality in patients treated with various products; however, only one study (4S) and one product (simvastatin) had been demonstrated to do so. Thus, to suggest that reduced total mortality was a class effect of all statins and was a function simply of cholesterol reduction alone was unfounded. In referring to the 1995 meta-analysis by Gould *et al* in its response, Parke-Davis should also have acknowledged that the authors recognised the limitations of their own work " ...Meta-analyses seldom, if ever, "prove" specific hypotheses." Indeed, they also noted that the 4S results exceeded their expectations based on their own model, "... the 42% reduction in CHD mortality observed in 4S was greater than the 29% reduction predicted by our model...". This served to illustrate the perils of reliance on meta-analyses over the hard results of clinical trials.

Merck Sharp & Dohme pointed out that Parke-Davis further claimed that "broadly similar clinical benefits" had been seen in three studies using simvastatin, pravastatin and fluvastatin respectively. Merck Sharp & Dohme believed this assertion to be incorrect as the only study of the three which demonstrated a statistically significant decrease in total mortality was 4S using simvastatin. If, as Parke-Davis claimed, this was a class effect, then Merck Sharp & Dohme would expect to see these benefits feature in the licensed indications of all three products. They did not. Only Zocor had a licensed indication to "... reduce the risk of mortality" in CHD patients.

In Merck Sharp & Dohme's view, Parke-Davis seemed to base its comments on supposition and hypotheses, "... it would be hard to imagine a substantial difference within the class..." and "... the physician will be basing his/her decision to prescribe on the scientific merit of the data of all sources...". Merck Sharp & Dohme would prefer to draw the Appeal Board's attention to the actual views of a clinician reviewing the data. In the Jackson editorial (referred to in Merck Sharp & Dohme's appeal and see below), the editor stated "The newest statin atorvastatin, reduces LDL cholesterol by 25 - 60% and triglycerides by up to 30%. However, as can be seen from the above, this will not be relevant for the average patient who makes up 80% of those eligible for therapy. It is vitally important to remember that the clinical not the biochemical benefit is our endpoint and we must not be seduced by bigger and better biochemical results if they have no clinical meaning. A sledgehammer is rarely needed to crack a nut. While atorvastatin will be of undoubted value in the more severe cases there will be no mandate to change from the tried and tested statins (fluvastatin, lovastatin, pravastatin and simvastatin) as they have been shown to, and will continue to, benefit the majority. The only mandate for change would be evidence on the scale of CARE, 4S and WOSCOPS that atorvastatin was superior due to its potency, and that will mean head-to-head trials."

ii) Use of the Helsinki Heart Study Merck Sharp & Dohme believed Parke-Davis might have misunderstood its comments on this study. Merck Sharp & Dohme was making the simple point that, while reduced levels of cholesterol in that study might have shown reduced CV events, it did not lead to a reduction in total (all cause) mortality, but a small increase in the level of total mortality. It was therefore inaccurate to make the generalisation that "... reducing cholesterol levels" automatically leads to "reduced total mortality" as the detail aid implied. Given the wide differences in terms of patient populations, therapies used and results seen between the various studies quoted, this was hardly surprising. Merck Sharp & Dohme's point was that each study must be taken on its own merits and great care must be exercised in seeking to generalise these results. Merck Sharp & Dohme did not believe that Parke-Davis had taken sufficient such care.

iii) Other effects of statins Again, Merck Sharp & Dohme believed that Parke-Davis might have missed Merck Sharp & Dohme's point. There was a wide body of medical opinion (exemplified by Jackson and Vaughan) that the clinical benefits seen with statin therapy might not simply be due to reductions in LDL-cholesterol. Merck Sharp & Dohme did not intend to convey the impression that these other factors would operate to the exclusion of such LDL reductions; however, the precise interplay between them was not yet established. Merck Sharp & Dohme therefore believed that it had been established that it was misleading to promote a pharmaceutical product on the basis that all the benefits quoted in the detail aid were the result simply of reducing cholesterol levels.

iv) Use of Merrill Lynch data Merck Sharp & Dohme did not believe that this data was a credible support for Parke-Davis' view that reduced morbidity and mortality were class effects of statins.

Merck Sharp & Dohme referred to the details of the market research presented. Firstly, it was based on a sample of 40 physicians. Given the sweeping nature of the generalisations which were based on it, Merck Sharp & Dohme believed this sample size to be inadequate. In addition, the critical findings were simply presented as "... Merck's message ..., is being weakened by a perception that this is a class effect and not unique to ZOCOR."

Merck Sharp & Dohme had no idea what questions were posed to the informants, nor what their actual answers were. Merck Sharp & Dohme drew the Appeal Board's attention to the BPMRG/ABPI Guidelines on Pharmaceutical Market Research Practice. Merck Sharp & Dohme believed that any market research, used either in promotion or to support promotional statements, should comply with these Guidelines. Also, it was for the party seeking to rely on the market research to demonstrate that it did so comply. On the basis of the reference provided by Parke-Davis, Merck Sharp & Dohme had no way of knowing whether the research complied with the Guidelines or not. In fact, there was so little detail that Merck Sharp & Dohme did not know which particular provision it should draw to the Appeal Board's attention. In particular, Merck Sharp & Dohme pointed out that it had no idea whether the requirements of Guidelines 2.3, 4 and 6 had been observed.

So far as the letter from the 4S investigator was concerned, Merck Sharp & Dohme submitted a further letter from him. He made it quite clear in this letter that his previous comments had been, at least, misinterpreted by Parke-Davis. His view was that the clinical benefits seen with other statins, particularly in this case simvastatin, might eventually prove to be common to the class, but that this must be demonstrated in clinical trials before it could be claimed. While he applauded atorvastatin's ability to lower lipid levels, he did not believe that this alone automatically led to other clinical benefits. This was entirely consistent with Merck Sharp & Dohme's view throughout. The current state of understanding about the clinical benefits of cholesterol reduction was progressing but it was both premature and incorrect to talk about "class effects" amongst the statins.

v) Comparative outcomes data For the reasons set out above, Merck Sharp & Dohme did not believe that "cholesterol lowering had been shown to improve clinical outcome by virtue of reduction in cardiovascular mortality and morbidity and overall mortality". Despite the number of studies having been undertaken which were powered to demonstrate reductions in both cardiovascular and overall mortality, only one study had managed, in fact, to demonstrate a reduction in overall mortality. If these were to be class effects one would have anticipated that they would be demonstrated in virtually every study powered to show them. This had not occurred and they could not therefore be said to be class effects. If Parke-Davis wished to claim these clinical benefits for atorvastatin, it must undertake appropriately powered clinical studies approved by the relevant ethics committees. Merck Sharp & Dohme did not envisage that such a study would use placebo as its control group; however, Merck Sharp & Dohme could see no reason why it should not compare atorvastatin and simvastatin. Merck Sharp & Dohme found it rather revealing that the respondent did not seem to be contemplating such a study.

vi) General Merck Sharp & Dohme referred to Parke-Davis' view that the Panel accepted that improved survival was a class effect of all statins "arising out of their cholesterol lowering effects". This was not so. The Panel's finding was based on the fact that "It was made clear that no studies used atorvastatin" and "The Panel did not accept that because Lipitor had no data on the end points of reducing morbidity and mortality, the failure to recognise this in the claim misled the reader". This was quite different from the Panel making a specific finding that the scientific evidence supported extrapolating these "benefits" to atorvastatin, which it seemed Parke-Davis was now claiming.

Throughout its response, Parke-Davis also claimed that it had not sought to "promote Lipitor as better than simvastatin with regard to clinical outcome...". Merck Sharp & Dohme did not believe this to be the case. In the detail aid which was the subject of Merck Sharp & Dohme's complaint, the Appeal Board's attention was drawn to the first four pages. The first page was clearly promotion for atorvastatin. The second page gave details of four clinical outcomes which Parke-Davis claimed were "The benefits of reducing cholesterol levels", and which it had subsequently claimed to be class effects common to all statins. The next page contained two quotations which were clearly intended to reinforce in the clinician's mind the connection between these "benefits" and the degree of cholesterol reduction achieved, and the following page then claimed that atorvastatin was capable of reducing cholesterol to a greater extent than other available statins. It was clearly the intention of these four pages to lead the physician to conclude that treatment with atorvastatin would provide (at least) similar clinical outcomes to those which had been demonstrated with other products. This went beyond merely seeking to place a new product in its correct clinical context and was, again, a breach of Clause 7.2 of the Code.

APPEAL BOARD RULING

The Appeal Board noted that page 2 of the detail aid highlighted the benefits of reducing cholesterol levels giving details of the various studies and the agents used in each study. Page 3 referred to "The need for greater efficacy". The Appeal Board noted the response from the company's representatives to a question about this page that there was a clinical need to lower cholesterol further in certain patient groups.

The Appeal Board did not accept that it was unreasonable for the detail aid to refer to benefits of reducing cholesterol levels in various studies. It was made clear that none of the studies used atorvastatin. The Appeal Board did not accept that the detail aid was misleading in this regard.

The Appeal Board did not accept that because Lipitor had no data on the end points of reducing morbidity and mortality, the failure to recognise this misled the reader.

The Appeal Board upheld the Panel's ruling of no breach of Clause 7.2 of the Code.

The appeal therefore failed.

2 Claim: "It is easy to see why new Lipitor outclasses the competition"

COMPLAINT

Merck Sharp & Dohme alleged that this claim was in breach of Clauses 7.2, 7.3 and 7.8 as it was an exaggerated claim which was misleading, inaccurate and could not be substantiated. Merck Sharp & Dohme noted that Parke-Davis had offered to withdraw the claim from future promotional items and thus, should the offer still hold, the matter was brought to the Authority's attention for the sake of completeness only.

RESPONSE

Parke-Davis said that in a spirit of compromise it voluntarily agreed not to use the word "outclasses" in future promotional material.

PANEL RULING

The Panel considered that, as Parke-Davis had agreed not to use the word "outclasses", Merck Sharp & Dohme had not made a formal complaint about the matter. The Panel therefore did not make a ruling.

B BROCHURE (Z590/90026B)

3 Claim: "The most effective cholesterol lowering agent"

The allegation concerning this claim had been covered in point 1 above.

4 Claim: "Lipitor. A new statin that outclasses other statins"

The allegation concerning this claim had been covered in point 2 above.

5 Claim: "Strength.....never before seen in statin therapy"

COMPLAINT

Merck Sharp & Dohme said that, as outlined above, statements such as this could only be made based on head to head studies comparing atorvastatin with all other statins where the results of the studies were freely available. Breaches of Clauses 7.2, 7.3 and 7.8 of the Code were alleged. There was inadequate data to support these all embracing claims as no data had been shown generated from direct head to head studies comparing atorvastatin with other statins.

RESPONSE

Parke-Davis submitted that the campaign for Lipitor revolved around the statement "Strength, Range and Simplicity never before seen in statin therapy". The benefits were supported by specific qualities of the products. The statement "never before seen in statin therapy" which followed the description of the benefits clearly referred to the combination of the benefits, strength, range and simplicity, which in aggregate had not previously been achieved by any statin in the UK.

Parke-Davis said that Merck Sharp & Dohme had chosen in a rather contrived fashion to examine individual benefits separately in conjunction with the strap line and in this regard contended that certain of the characteristics attributed to Lipitor had been seen before with other statins. In particular, that treatment with simvastatin enabled a similar percentage of patients to reach their EAS treatment goals and that, since treatment with all other statins was also one tablet daily, that claiming "simplicity" in respect of the dosage of Lipitor was inaccurate.

The strap line "...never before seen in statin therapy" only appeared with the combination graphic depicting strength, range and simplicity and it was clear that it referred to the combination. The evidence demonstrated that Lipitor was the most effective agent at lowering cholesterol (point 1 above). Coupled with this superior strength was the fact that Lipitor had a broader range of indications when compared with the other statins (point 7 below). Lipitor had been licensed to reduce cholesterol, LDL-cholesterol and triglycerides in patients with primary hypercholesterolaemia, mixed hyperlipidaemia and homozygous familial hypercholesterolaemia. In the brochure the statement "Simplicity to bring 70 - 90% of patients to their EAS treatment goals with the 10mg starting dose" was simply a statement of fact. It did not appear with the strapline and the company was not suggesting that simvastatin or any other statin did not allow a substantial percentage of patients to achieve their treatment goals with a once daily dosage. The argument raised by Merck Sharp & Dohme that Parke-Davis was claiming a one tablet per day "simplicity" never before seen in statin therapy was spurious and totally incorrect. Most doctors knew that all the marketed statins were available in a single daily dose. It was senseless to suggest that Parke-Davis had an interest in misleading doctors about this. The tablet element of the graphic in the advertisement depicted a tablet in the palm of a hand with a statement " to bring 70 - 90% of patients to their EAS treatment goals with the 10mg once daily starting dose" directly underneath. The graphic was suitably qualified and demonstrated that Lipitor had the ability to bring 70 - 90% of patients to their EAS treatment goals with the 10mg starting dose, thus reducing the need for multiple visits to titrate the dose. It was this, in combination with Lipitor's strength and range to treat more profiles, which had never before been seen in statin therapy.

In respect of the detail aid, the elements of the graphic were explained inside, the tablet graphic represented the starting dose and was linked with achieving treatment goal success and tolerability. There was no implication in this or any other part of the promotion that Lipitor was different from any of the other statins in having a once a day dosage.

With regard to the claim "Strength .... never before seen in statin therapy", Parke-Davis submitted that the statement was only part of the claim. The graphic associated with strength related to the simple ability of the product to reduce cholesterol and triglyceride levels more than any other statin. The company referred to its response in point

1 above.

The results of the clinical trials with Lipitor demonstrated that Lipitor possessed greater LDL-cholesterol lowering properties than the currently available statins. The level of efficacy at lowering cholesterol was unrivalled by any other cholesterol lowering medicine available in the UK. Atorvastatin monotherapy reduced LDL-cholesterol between 40 to 60% across its dosage range. Even at Lipitor's 10mg starting dose cholesterol levels were likely to be reduced more than with maximum doses of other statins. The other statins currently available reduced LDL-cholesterol by 20 to 40% throughout their currently approved dosage range.

PANEL RULING

The Panel noted that there was some confusion between the brochure, the detail aid and the journal advertisement in relation to the claims at issue. The front page of the brochure and the front page of the detail aid were identical. There appeared to be no separate allegations about the detail aid although it was referred to by Merck Sharp & Dohme in some of the allegations (point 1 and point 5). The allegations regarding the journal advertisement were dealt with under C below.

The front page of the brochure was headed " New Lipitor" and this was followed by three illustrations, one labelled strength, one labelled range and one labelled simplicity. The visual labelled simplicity was of a palm of a hand with one tablet in it. The illustrations were followed by the claim "... never before seen in statin therapy". The Panel considered that the layout of this page was such that the three features of strength, range and simplicity were the features never before seen in statin therapy. It decided therefore not to rule separately on each point as alleged by Merck Sharp and Dohme (points 5, 6 and 7) but to rule on the page as a whole (see point 7 below).

6 Claim: "Range ... to treat more profiles than any other statin"

COMPLAINT

Merck Sharp & Dohme alleged that this claim was in breach of Clauses 7.2, 7.3 and 7.8. The range of patient profiles and the licensed indications for atorvastatin were no greater than were included in the licensed indications for the other statins. All statins were licensed for use in patients with primary hypercholesterolaemia. Atorvastatin had an additional unique claim to lower cholesterol for a small number of patients who fitted special sub-populations within this group of primary hypercholesterolaemic patients. However, it did not have an indication to reduce morbidity and mortality in a much larger patient population, those with coronary artery disease. Simvastatin was uniquely indicated in patients with coronary heart disease to reduce the risk of mortality and morbidity. Pravastatin had specific indications for the prevention of coronary heart disease. These two drugs therefore had licensed indications for treating a different and much wider range of patients.

It was therefore misleading to suggest that atorvastatin had a range to treat more profiles than either simvastatin or pravastatin. Both simvastatin and pravastatin had different licensed indications, which were in a number of respects different from atorvastatin, and thus atorvastatin was not "broader" than the others.

RESPONSE

Parke-Davis said that the allegation turned upon Merck Sharp & Dohme's attempt to confuse the issue of different lipid profiles with different disease states. Lipitor was indicated in patients unresponsive to diet and other non-pharmacological measures for the reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B and triglycerides in patients with primary hypercholesterolaemia, heterozygous familial hypercholesterolaemia or combined (mixed) hyperlipidaemia. Lipitor was also indicated for the reduction of elevated total cholesterol, LDL-cholesterol and apolipoprotein B in patients with homozygous familial hypercholesterolaemia.

Lipitor had the broadest licensed indications within the statin class and was specifically licensed for use in patients with raised triglycerides as well as raised cholesterol levels (mixed hyperlipidaemia).

Contrary to the suggestion of Merck Sharp & Dohme that Lipitor's additional unique claim to lower cholesterol was only for a small number of patients who fitted special sub-populations within this group of primary hypercholesterolaemic patients, mixed hyperlipidaemia was the most common lipid abnormality seen in individuals with coronary heart disease. Sixty per cent of patients with raised cholesterol also had raised triglycerides ie mixed hyperlipidaemia . Moreover, Lipitor was the only lipid modulating drug to be licensed for the treatment of patients with homozygous familial hypercholesterolaemia. Thus it was clear that Lipitor treated more patients with more lipid profiles than currently available statins in the UK. A copy of the summary of product characteristics for Lipitor was provided.

Parke-Davis submitted that Merck Sharp & Dohme was deliberately confusing the range of lipid disorders that might be treated with Lipitor with the number of patients with coronary artery disease who might be treated to reduce morbidity and mortality. It must be noted that these secondary prevention groups would only be treated if they also had a lipid disorder, hence the actual number of those patients that could be treated could not be increased by virtue of a secondary prevention licence. Clearly, simvastatin, pravastatin and fluvastatin had not been shown to be effective in patients with homozygous familial hypercholesterolaemia, but, more importantly, they were not approved for use in patients with raised triglycerides as well as raised cholesterol (mixed hyperlipidaemia). Lipitor was approved for use in both these additional patient populations and therefore, by definition, Lipitor had the range to treat more patients and more profiles than other statin.

For Panel ruling - see point 7 below.

7 Claim: "Simplicity ... never before seen in statin therapy"

COMPLAINT

Merck Sharp & Dohme alleged that this claim was in breach of Clause 7.2 as it was inaccurate. The picture with the caption showed a once a day tablet and clearly implied that atorvastatin was different from the other statins having a one tablet daily dosage. Simvastatin had been licensed as a once daily dose for seven years. Furthermore, all the currently available doses of simvastatin were one tablet once a day.

RESPONSE

Parke-Davis' response covered both point 7 and point 8 below.

Parke-Davis said that the statement "...never before seen in statin therapy" referred to the combination of strength, range and simplicity afforded by Lipitor. Merck Sharp & Dohme alleged that the claim for percentages of patients reaching their EAS treatment goals was misleading and did not represent the body of evidence available. Further, Merck Sharp & Dohme said that 72% of patients treated with a single dose of simvastatin in the 4S study reached their EAS treatment goals. This was not with the licensed starting dose (10mg/day) but with doses of 20 or 40mg of simvastatin daily. This was clearly not the level of simplicity that Parke-Davis was able to claim and substantiate for Lipitor.

The claim "... to bring 70 - 90% of patients to their EAS treatment goals with the 10mg once daily starting dose" was generated from data combined from three separate comparative studies involving atorvastatin, lovastatin, pravastatin and simvastatin. However, it was important to note that the original study treatment goals were based on the American National Cholesterol Education Programme (NCEP) target goals and the data were retrospectively reassessed according to the EAS treatment goal guidelines. The study protocols allowed for the dosage to be increased after 16 weeks if the therapy goals had not been achieved. However, to illustrate the claim that 70 - 90% of patients reached EAS treatment goals with the starting dose of Lipitor therapy, data were only presented for 16 weeks where patients received either the starting dose of atorvastatin (10mg once daily), simvastatin (10mg once daily), pravastatin (20mg once daily) or lovastatin (20mg once daily). This was clearly communicated to Merck Sharp & Dohme on several occasions. In making the allegation Merck Sharp & Dohme had completely ignored all the explanations and information provided explaining exactly how the 70 - 90% figure was obtained. Merck Sharp & Dohme stated that the published data from four abstracts actually showed that between 46% and 74% of patients had achieved their LDL-cholesterol treatment goal. This was not disputed but Merck Sharp & Dohme had purposely missed the point by using the general term "treatment goal". The percentage figures quoted in the abstracts and research reports for the above mentioned studies related to the percentage of patients achieving the American NCEP guidelines and not the European EAS guidelines. Data was provided regarding the pooling of the studies.

Parke-Davis submitted that the three studies were appropriately selected for pooling because they were of similar design and methodology; a study could not be added simply by virtue of the fact that it had been presented in abstract form. The design of the Wagner one year, intent-to-treat study of atorvastatin versus pravastatin was dissimilar to the three other studies pooled. The Wagner study used starting doses of atorvastatin and pravastatin that were not included in the other protocols and involved the titration of patients according to different criteria at different time points. Parke-Davis maintained that the Wagner study was justifiably excluded for scientifically valid reasons and not simply because it might not have supported the claim. Nevertheless, in the spirit of co-operation and compromise, Parke-Davis accepted Merck Sharp & Dohme's suggestion regarding the analysis of the Wagner data at either 8 or 16 weeks with regard to the number of patients that achieved their EAS treatment goals whilst receiving atorvastatin 10mg daily or pravastatin 20mg daily.

That analysis had been completed by US colleagues. Data had been combined across the four studies and the percentages of patients who met their EAS LDL-cholesterol goal were assessed by treatment group within each category (high, moderate and mild risk). The results for the high and moderate risk patients (the categories from which the figures of 70% and 90% were originally derived) were provided. As anticipated, the analysis including the Wagner data had not significantly altered the previous figures. The number of high risk patients achieving their EAS goal was slightly reduced from 70% to 67% but the number of moderate risk patients achieving their EAS goal was actually increased to 95%. Should the Authority consider it absolutely necessary, the company would consider adjusting the figures in the claim to reflect the four study analysis but submitted that it was not necessary to do so.

Parke-Davis was not suggesting that simvastatin or any other statin did not allow a substantial percentage of patients to achieve their treatment goals with a once daily dosage. The strap line "... never before seen in statin therapy" referred to the three Lipitor characteristics of strength, range and simplicity in aggregate and therefore it was this combination that had not been seen before in statin therapy.

Accordingly, the claim could be substantiated, it was balanced and fair and not ambiguous, exaggerated or all-embracing in any way.

PANEL RULING

The Panel considered that there was data to support the claim "Strength...never before seen in statin therapy". This was the data referred to in point 1 above.

The Panel noted that the statins had different licensed indications. Lipitor was indicated as an adjunct to diet for reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B and triglycerides in patients with primary hypercholesterolaemia, heterozygous familial hypercholesterolaemia or combined (mixed) hyperlipidaemia when response to diet and other non pharmacological measures was inadequate. In addition Lipitor was also indicated as an adjunct to diet and other non-dietary measures in reducing elevated total cholesterol, LDL-cholesterol and apolipoprotein B in patients with homozygous familial hypercholesterolaemia when response to these measures was inadequate.

Zocor (simvastatin) was licensed for use in patients with primary hypercholesterolaemia in whom response to diet and other non pharmacological measures had been inadequate. It was also licensed for use in patients with coronary heart disease with a plasma cholesterol level of 5.5mmol/l or greater (ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1996-97). Zocor was unlikely to be of clinical benefit in homozygous familial hypercholesterolaemia in patients with a complete absence of LDL receptors. Zocor had only a moderate triglyceride lowering effect and was not indicated where hypertriglyceridaemia was the abnormality.

Lipostat (pravastatin) was indicated for the reduction of elevated total and LDL-cholesterol levels in patients who had not responded adequately to dietary measures. It was also licensed as an adjunct to diet to slow the progressive course of coronary artherosclerosis and reduce the incidence of clinical cardiac events in patients with hypercholesterolaemia and documented artherosclerotic coronary artery disease and also as an adjunct to diet in hypercholesterolaemic patients without clinically evident coronary heart disease. Lipostat should not be used in patients with elevated HDL-C or those with homozygotic familial hypercholesterolaemia.

Lescol (fluvastatin) was indicated in primary hypercholesterolaemia in patients who did not adequately respond to dietary control. Lescol was unlikely to be of benefit in patients with rare homozygous familial hypercholesterolaemia.

Both simvastatin and pravastatin were licensed for use in coronary heart disease in patients with hypercholesterolaemia. In the Panel's view this was not an indication additional to the indication for hypercholesterolaemia.

In the Panel's view Lipitor was licensed to treat more profiles than the other statins. It accepted the submission from Parke-Davis on this point.

The Panel did not accept that the claim "Simplicity .... never before seen in statin therapy" implied that atorvastatin was different from all the other statins having a one tablet daily dosage.

Overall the Panel considered that the page in the brochure (which was the same as the page in the detail aid) was acceptable. No breach of the Code was ruled. This ruling covered points 5, 6 and 7. Merck Sharp & Dohme appealed in relation to point 5 - see below.

8 Claim: "Simplicity to bring 70 - 90% of patients to their EAS treatment goals with the 10mg once daily starting dose".

This claim appeared on the penultimate page of the brochure.

COMPLAINT

Merck Sharp & Dohme alleged that this claim breached Clauses 7.2, 7.3 and 7.8. The claim for percentages of patients reaching their EAS treatment goals was misleading as it did not represent the body of available evidence. It was derived from an amalgamation of three separate studies (Bakker-Arkema, Egros and Bracs) but excluded one large study (Wagner). The published data from these four studies actually showed that 46 - 74% had achieved the LDL treatment goals. This fell far short of the promotional claim of 70 - 90% of patients reaching treatment goals, which was therefore an exaggerated claim.

In the 4S study (comparing 4444 post-MI and angina patients treated with Zocor or placebo over a median of 5.4 years) it was demonstrated that 72% of patients had been brought to their EAS treatment goals with a once daily dosage of a statin (simvastatin). This achievement of over 70% of patients in trials of statin therapy reaching treatment goal had indeed been seen before.

RESPONSE

Parke-Davis' response was given in point 7 above.

PANEL RULING

The Panel noted that the figures of 70 - 90% were generated from data combined from three separate studies (Bakker-Arkema, Egros and Bracs) which had been reworked according to EAS treatment goals. The Wagner study was excluded as the design and methodology differed from the other three. When the Wagner data was reworked and included with the other three studies the range was 67 - 95%. The Panel accepted that there were methodological reasons for using only three studies and that the resulting percentages were very similar if the Wagner data were included. In the circumstances it was not misleading to use the range 70 - 90% and the Panel ruled no breach of the Code.

9 Claim: "Lipitor lowers cholesterol levels to a significantly greater extent than other currently available statins"

This claim appeared on page 2 of the brochure next to a graph showing the percentage change in LDL-cholesterol for various doses of fluvastatin, pravastatin, simvastatin and Lipitor. A statement "Comparison derived from a published review of independent studies" appeared next to the graph.

COMPLAINT

Merck Sharp & Dohme alleged that the claim, taken in association with the accompanying graph, was in breach of Clauses 7.2, 7.3, 7.8 and 8.1 as the claim was not balanced or fair, not capable of substantiation, included a superlative, was disparaging to other products and did not present the data in a clear, fair and balanced way.

The claim was for superior potency in relation to weight, without link to some practical advantage. As discussed, there was insufficient data from true head to head comparisons of the effects of various doses of atorvastatin with equipotent (ie clinically equivalent) doses of simvastatin to support this claim. The graph was highly misleading as the data depicted was not taken from head to head studies. Data was derived from a variety of different studies with different designs. These ranged, for example, from a 6 week phase II dose ranging study in small numbers of patients to large phase III studies in many patients. Merck Sharp & Dohme was particularly

concerned that there was no indication that these were not head to head comparisons and that there was no indication that equipotent doses were not being compared and nor was there indication of any statistical significance of the effect of cholesterol lowering.

RESPONSE

Parke-Davis submitted that the data already presented fairly reflected the results of available research and fully substantiated the claims made with regard to the greater cholesterol lowering effect of Lipitor. The claim was balanced and fair and not ambiguous, exaggerated or all-embracing in any way. It accurately reflected the reported LDL-cholesterol lowering effects of the current statin drugs available in the UK and did not disparage other companies' products. Parke-Davis had asked Merck Sharp & Dohme if it knew of any data which existed, and of which it was unaware, which might support greater than 40% LDL-cholesterol lowering with approved doses of simvastatin and would show that this was not a fair representation. It had not responded to date.

With regard to the data depicted in the graph in the brochure, it was expressly stated that the data were derived data from independent studies and represented the LDL-cholesterol lowering effect of the statins at each approved dosage (except for fluvastatin which was licensed for use at 80mg daily after the article was published). Moreover, the graph accurately reflected the data reported for the other statins in the Physicians Desk Reference (these were data supplied by all of the approved statin manufacturers in the USA) and no attempt had been made to misrepresent the information in anyway. The claim was that Lipitor was more effective at lowering cholesterol than any other currently available statin. Efficacy was the absolute ability of an agent to produce a given pharmacological effect. Merck Sharp & Dohme was deliberately confusing potency and efficacy and argued that this was purely a claim for superior potency in relation to weight, without link to some practical advantage. Potency referred to a pharmacological effect achieved per unit dose and equipotent drugs produced the same effects at the same milligram doses. Notwithstanding that Parke-Davis was not making a potency claim, this was clearly not the case with Lipitor and simvastatin, where equivalent milligram dosages produced very different cholesterol lowering effects. Ten milligrams of atorvastatin lowered cholesterol to a similar degree to 20 - 30mg of simvastatin. One US clinician had reported that the product "... appears to be about 50% more powerful than simvastatin" and in actual fact this view was supported by the MCA's clinical assessor for Lipitor. It was important to note, however, that no claims were made about potency which the industry generally regarded as an inappropriate method of promotion. The promotion was based on efficacy and the fact that a level of efficacy not previously seen had been demonstrated.

PANEL RULING

The Panel considered that Parke-Davis had data to support the claim "Lipitor lowers cholesterol levels to a significantly greater extent than other currently available statins. Parke-Davis had provided comparative data in its response to point 1 above. No direct comparative data had been provided in relation to fluvastatin. The claim did not use a superlative. The Panel did not consider that the graph amounted to a claim for superior potency in relation to weight. No breach of the Code was ruled.

The graph was taken from a review by Black (1995). The graph was clearly labelled as being from a published review of independent studies. The Panel did not accept that the graph was misleading. No breach of the Code was ruled. Merck Sharp & Dohme appealed in relation to this point - see below.

C JOURNAL ADVERTISEMENT (Z596/90036A)

The advertisement had a different layout to the brochure with regard to the claims strength, range and simplicity. The journal advertisement was headed "New Lipitor" followed by the headings "Strength", "Range" and "Simplicity" each followed by a graphic. Unlike the brochure each graphic was followed by a claim. "Strength" was followed by the claim "to reduce cholesterol and triglycerides more than any other statin". "Range" was followed by the claim "to treat more profiles and more patients than any other statin". "Simplicity" was followed by the claim "to bring 70 - 90% of patients to their EAS treatment goals with the 10mg once daily starting dose". Across the page was the claim "... never before seen in statin therapy".

10 Claim: "The most effective cholesterol lowering agent"

The allegation concerning this claim had been covered in point 1 above.

11 Claim: "Strength - to reduce cholesterol and triglyceride levels more than any other statin"

The allegation concerning this claim had been covered in point 5 above and was appealed by Merck Sharp & Dohme - see below.

12 Claim: "Range ... to treat more profiles than any other statin"

The allegation concerning this claim had been covered in point 6 above.

13 Claim: "Simplicity to bring 70 - 90% of patients to their EAS treatment goals with the 10mg once daily starting dose ... never before seen in statin therapy"

The allegation concerning this claim had been covered in point 8 above.

APPEAL BY MERCK SHARP & DOHME OF POINTS 5, 9 AND 11

Claims 5, 9 and 11. "Strength... never before seen in statin therapy" and related claims.

Merck Sharp & Dohme believed that this claim breached Clause 7.2 of the Code because it made a misleading

comparison between atorvastatin and all other statins.

The claim, together with the graph on page 2 of the brochure, were based on a review by Black *et al* which selectively presented the best results for atorvastatin and compared them with particularly poor results for simvastatin. This data was based on early studies, with small numbers of patients, which had clearly been surpassed by more recent large-scale trials for Zocor and clinical experience over almost eight years of licensed usage. For example, in the 4S study, 20mg of Zocor lowered LDL-cholesterol by 35%. The study by Bracs *et al* showed reductions in LDL-cholesterol at 52 weeks of 32% and 33% with 10mg and 20mg of Zocor respectively and of 38% with both 10mg and 20mg of atorvastatin. Merck Sharp & Dohme believed this to be clinically more appropriate than the Black study because it was a head-to-head trial, and gave a more accurate comparison of the effects of the two drugs at dosages which were expected to be commonly prescribed. Davidson *et al* demonstrated a decrease of 41% in LDL-cholesterol with 40mg of Zocor.

Merck Sharp & Dohme accepted that a difference between the two lines on the graph would still exist, even if the data from 4S, Bracs and Davidson were used. However Merck Sharp & Dohme believed that the use of the Black study in particular was driven by a desire to enable representatives to claim that the starting dose of atorvastatin delivered LDL-cholesterol reductions only seen at the maximum licensed dosages of other statins. Support for this view was gained from the statement from Parke-Davis in its response to the complaint, "Even at Lipitor's 10mg starting dose cholesterol levels were likely to be reduced more than with maximum doses of other statins". There was no comparative data available to support this contention.

Merck Sharp & Dohme maintained that insufficient evidence had been provided by Parke-Davis to substantiate the claim and that it would mislead readers and so was in breach of Clause 7.2.

RESPONSE FROM PARKE-DAVIS

Parke-Davis pointed out that Merck Sharp & Dohme suggested that the claim was based solely on a review by Black but this was incorrect. As Parke-Davis had already fully described, the results of the clinical trials with Lipitor demonstrated that Lipitor possessed greater LDL-cholesterol lowering properties than the currently available statins. Lipitor monotherapy (10 to 80mg daily) reduced LDL-cholesterol between 40 - 60% across its dosage range; even at Lipitor's 10mg starting dose, cholesterol levels were likely to be reduced more than with maximum doses of other statins. The other statins currently available reduced LDL-cholesterol by 20 - 40% throughout their currently approved dosage range.

Merck Sharp & Dohme contended that the Black study selectively used the best results for Lipitor and compared them with particularly poor results for simvastatin. This was simply not the case. The review article by Black took data from the Physician's Desk Reference in the US (the article by Black being published in an American journal), and it was expressly stated that the data presented were data derived from independent studies and represented the LDL-cholesterol lowering effect of the statins at each approved dosage (except for fluvastatin which was licensed for use at 80mg daily after the article was published). Similar figures for Lipitor were extracted from the package insert in the US and this would appear in subsequent editions of the Physicians' Desk Reference. These data accurately reflected the reported LDL-cholesterol lowering effects of the current statin drugs available. Parke-Davis, in fact, asked Merck Sharp & Dohme if it knew of any existing data of which Parke-Davis was unaware and which might support greater than 40% LDL-cholesterol lowering with approved doses of simvastatin and which might therefore suggest that this was not a fair representation. It had not responded and, to date, Parke-Davis remained unaware of any information which would lead it to believe that this representation of LDL-cholesterol lowering with the various statins at licensed dosages was incorrect.

Merck Sharp & Dohme had also raised points from two studies. Firstly, the figures it quoted from the study by Bracs (now published as Dart A *et al*) showed LDL-cholesterol reductions of 37% with 10mg daily Lipitor compared to 30% with 10mg daily of simvastatin at 16 weeks (p=0.0011). The dose of each statin was doubled at week 16 if any patient's LDL-cholesterol level was still above the treatment goal of 3.4mmol/l. At the end of the study the mean percentage decrease in LDL-cholesterol from baseline was 38% for atorvastatin compared to 33% for simvastatin. This difference remained highly statistically significant (p=0.0036). To quote an extract from the efficacy results: "At week 52, the adjusted mean percent decrease in LDL-cholesterol from baseline remained significantly greater for atorvastatin (Lipitor) than for simvastatin (38% vs 33%), despite a greater proportion of patients being titrated up in dose with simvastatin (p=0.0036)". Secondly, the data Merck Sharp & Dohme cited by Davidson *et al* did not demonstrate that Parke-Davis' claim was inaccurate or misleading; Parke-Davis had acknowledged that maximum doses of simvastatin could bring LDL-cholesterol reductions of up to 40% in short-term studies. Merck Sharp & Dohme itself accepted that a difference in LDL-cholesterol lowering would still exist even if data from 4S, Bracs and Davidson were used. Parke-Davis did not believe therefore that this claim could be considered to breach Clause 7.2 of the Code.

With regard to the data depicted in the graph in the brochure and its usage, Parke-Davis stressed that it had not misrepresented the information contained in it in anyway whatsoever. The graph was merely used to convey the fact that Lipitor was more effective at lowering cholesterol than any other currently available statin. Parke-Davis' aim had only ever been to focus upon the available data on the effect of statins, including Lipitor, on lowering cholesterol levels.

Merck Sharp & Dohme finally claimed that there were no comparative data available to support Lipitor's claim of superior efficacy. Parke-Davis believed that the mass of data that it had already presented fully supported its promotion which was based on the fact that it had demonstrated a level of efficacy at lowering cholesterol not previously seen. Furthermore, Parke-Davis would like to reiterate that the campaign for Lipitor revolved around the composite statement "Strength, Range and Simplicity never before seen in statin therapy". Those benefits were then supported by specific qualities of the product. The

statement "...never before seen in statin therapy", which followed the description of the benefits, clearly referred to the combination - Strength, Range and Simplicity. These benefits, in aggregate, had not previously been achieved by any statin in the UK. This claim had been adequately substantiated and could not be considered to be in breach of Clause 7.2 of the Code.

FURTHER COMMENTS FROM MERCK SHARP & DOHME

Merck Sharp & Dohme said that the graph to which it had referred in its complaint was exclusively referenced to the Black study. Merck Sharp & Dohme believed that the Black study (a retrospective analysis) used particularly good data for atorvastatin and relatively poor data for simvastatin. The fact that the data had been taken from the Physician's Desk Reference was, in its opinion, irrelevant. In order to demonstrate that the graph was not a breach of Clause 7.2, Parke-Davis must show that it was based on "an up to date evaluation of all evidence and reflect that evidence clearly." Merck Sharp & Dohme had drawn Parke-Davis' attention to the fact that there was a good deal of more recent data in much larger studies which yielded poorer results for atorvastatin than those quoted in the graph, and better results for simvastatin. Merck Sharp & Dohme therefore believed that the graph was not an up to date evaluation of all the evidence, nor did it reflect that evidence clearly.

Merck Sharp & Dohme noted that Parke-Davis had again indicated that "... even at Lipitor's 10mg starting dose, cholesterol levels are likely to be reduced more than with maximum dose of other statins". This was not true of simvastatin. The Black study had, however, been deliberately chosen by the respondent to support this misleading impression in its graph. Merck Sharp & Dohme had already acknowledged that there would still be a difference between the lines had the more representative studies been used. It would, however, prevent Parke-Davis from making the claim, which had now been repeated and which clearly appeared in the graph, that 10mg of atorvastatin lowered LDL cholesterol to a greater extent than 40mg of simvastatin. Parke-Davis acknowledged that the maximum LDL reduction seen with 10mg of atorvastatin was 40%. The Davidson study showed a decrease of 41% in LDL cholesterol with 40mg of Zocor. Merck Sharp & Dohme therefore believed the graph must be misleading and therefore a breach of Clause 7.2 of the Code.

APPEAL BOARD RULINGS

The Appeal Board decided to rule on each claim separately.

5 Claim: "Strength...never before seen in statin therapy"

The Appeal Board considered that there was data to support the claim. This was the data referred to in point 1 above. The Appeal Board upheld the Panel's ruling of no breach.

The appeal therefore failed.

9 Claim: "Lipitor lowers cholesterol levels to a significantly greater extent than other currently available statins"

The Appeal Board considered that Parke-Davis had data to support the claim. Parke-Davis had provided comparative data in its response to point 1. The Appeal Board noted Parke-Davis' submission that simvastatin and pravastatin were well known to be more efficacious than fluvastatin. No direct comparative data had been provided in relation to fluvastatin. Parke-Davis had provided some direct comparative data at the appeal hearing which had been presented at a meeting in August 1997. The data had not been available at the time the material in question was used. The claim did not use a superlative. The Appeal Board did not consider that the graph amounted to a claim for superior potency in relation to weight. The Appeal Board upheld the Panel's ruling of no breach of the Code.

The graph was taken from a review by Black 1995. The graph was clearly labelled as being from a published review of independent studies. The Appeal Board did not accept that the graph was misleading. The Appeal Board upheld the Panel's ruling of no breach of the Code.

The appeal therefore failed.

11 Claim: "Strength - to reduce cholesterol and triglyceride levels more than any other statin"

The Appeal Board considered that this claim had been covered by its ruling in point 5 above.

Complaint received **8 April 1997**

Case completed **11 September 1997**

CASE AUTH/535/4/97

SERONO v ORGANON

Patient leaflet for Puregon

Serono made a number of allegations about a patient information leaflet for Puregon issued by Organon.

The Panel ruled no breach of the Code in relation to an allegation that the leaflet constituted an advertisement to the public for a prescription only medicine. The leaflet was specific for Puregon and the intended audience was patients prescribed Puregon. Despite leaflets being freely available in a fertility clinic, they had been distributed by Organon with verbal instructions that they should only be given to patients already prescriber Puregon. The Panel considered that Organon would be well advised to supply written instructions regarding the use of such leaflets in future.

The Panel ruled a breach of the Code regarding the use of the superlative "best" in the claim "Puregon is ... designed to offer you the best chance of pregnancy".

The Panel considered that a statement saying that certain urinary gonadotrophins, Humegon and Normegon, were "no longer supplied" amounted to saying that they were "no longer available" which was not true. A breach of the Code was ruled.

No breach of the Code was ruled regarding a statement that in former fertility medicines and Puregon the basic active ingredient, FSH, was the same. Puregon contained only FSH and although the former fertility medicines contained a mixture of FSH and LH it was true to say that the basic active ingredient in both was FSH.

Serono Laboratories (UK) Limited complained about a patient information leaflet on Puregon (Ref: 01573c) issued by Organon Laboratories Ltd. The leaflet was headed "Puregon Your *NEW* medication".

1 Advertising to the general public

COMPLAINT

Serono said that the text of the leaflet was clearly directed at patients. The opening sentence of the leaflet stated "Puregon is a new fertility drug manufactured by the latest technology and designed to offer you the best chance of pregnancy". The text included references to "your doctor" and lay language was used throughout the piece. Serono said that the leaflet was freely available in the fertility unit it had obtained it from and the text did not state that the information given was only for patients who had been prescribed Puregon. Serono alleged that the leaflet constituted an advertisement to the general public for Puregon, a prescription only medicine, in breach of Clause 20.1 of the Code.

RESPONSE

Organon said that the leaflets were sent to infertility specialists with the company's standard instructions for patient leaflets, that they were to be given to patients who had already been prescribed the medicine in question. These instructions were given verbally by representatives to the appropriate health care professional. Organon said that these instructions were in compliance with the supplementary information to Clause 20.2 of the Code.

Organon said that on this occasion the instructions were sent using its e-mail system. As they were standard instructions no written record was retained. Organon said that it would introduce procedures to ensure that written records of these instructions were retained in future.

PANEL RULING

The Panel noted that the supplementary information to Clause 20.2 of the Code stated that companies could provide health professionals with leaflets concerning a medicine with a view to their provision to patients to whom the medicine had already been prescribed, provided the leaflet was factual and non-promotional. The Panel considered that when distributing product specific patient information leaflets, companies must issue clear instructions to both their representatives and the health professionals in order to ensure their correct use.

The Panel noted that the leaflet in question was specific for Puregon and that Organon had supplied copies to fertility specialists with verbal instructions that they were to be given to patients who had already been prescribed Puregon. The Panel noted that there was no written record of the instructions provided by Organon regarding the distribution of the leaflets.

It was not clear to the Panel how the leaflets had ended up being made freely available in the fertility clinic. The fertility specialist might have put the leaflets in the fertility clinic in spite of instructions from the Organon representative that they were only to be given to patients already prescribed Puregon. Organon was not responsible for how the healthcare professional distributed the leaflets providing adequate instructions had been given. The Panel considered that verbal instructions were adequate although written instructions would have been preferable. The intended audience for the leaflet was patients already prescribed Puregon. In such circumstances the leaflet was not an advertisement to the general public. The Panel therefore ruled no breach of Clause 20.1 of the Code.

The Panel considered that in future Organon would be well advised to supply written instructions to healthcare professionals regarding distribution of such leaflets. Organon should also keep copies of instructions to representatives.

2 Claim "Puregon is ... designed to offer you the best chance of pregnancy"

COMPLAINT

Serono said that this claim could not be substantiated since it had not been given in the context of any specific indication or treatment procedure. There was inadequate scientific data to support the claim. A breach of Clause 7.3

was alleged. Serono alleged that the use of the superlative "best" was in breach of Clause 7.8.

RESPONSE

Organon said that although Puregon had been shown to be the best infertility treatment by the largest ever controlled infertility study, there was no intention that "best" was used as a hanging comparison here, but rather a "comforting" statement that a more effective substitute gonadotrophin had been developed. The 1,000 cycle IVF study unequivocally demonstrated that the efficacy of Puregon was superior to that of a urinary gonadotrophin: significantly more oocytes were retrieved ($p<0.0001$), more high quality embryos obtained ($p<0.0001$), and ultimately, after replacement of frozen thawed embryos, a higher ongoing pregnancy rate was found ($p=0.05$). The size of the study ensured that fairly modest treatment effects would have been detected with a high probability. Puregon's higher activity was also suggested by significantly lower cancellation rate for low response.

These findings were reflected in the summary of product characteristics for Puregon which stated that "Puregon was more effective that urinary FSH in terms of lower total dose and a shorter treatment period. Therefore it may be appropriate to give a lower dosage of Puregon."

Organon said that the statement "Puregon is a new fertility drug and designed to offer you the best chance of pregnancy" was not made in order to raise unfounded hopes of successful treatment nor made to be exaggerated or all-embracing but only represented the fulfilment of Organon Laboratories' intention to develop a product which offered the best chance of pregnancy.

Organon added that the SPC for Gonal-F (Serono's recombinant product) clearly stated that "the equivalency of the potency of Gonal-F and urinary FSH containing preparations has not been definitely proven. However, clinical assessment of Gonal-F indicated that its dosage, regimens of administration and treatment monitoring procedures should not be different from those currently used for urinary FSH-containing preparations". A copy of the SPC for Gonal-F was provided.

PANEL RULING

The Panel noted that there was no allegation that the claim "Puregon is ... designed to offer you the best chance of pregnancy" contained a hanging comparison. The allegations were that the claim could not be substantiated and incorporated a superlative.

The Panel ruled that the use of the superlative "best" was in breach of Clause 7.8 of the Code. The use of the word "best" in the claim was in breach of the Code whether or not the claim using it could be substantiated. It was not therefore necessary to consider the alleged breach of Clause 7.3.

3 Availability of urinary gonadotrophins

COMPLAINT

Serono alleged that the statement "Puregon has replaced Humegon, Normegon and Orgafol. This means that they are no longer supplied to your doctor or clinic pharmacy." was untrue and misleading in breach of Clause 7.2 of the Code. Serono said that both Humegon and Normegon were listed in the current BNF (March 1997) and that IMS figures for the GP sector in February 1997 confirmed sales of both products. Serono noted that the preparation date of the patient information leaflet was September 1996.

RESPONSE

Organon said that although IMS figures confirmed sales of Humegon and Normegon and although these products were listed in the current BNF, Organon had decided that they would be succeeded by Puregon. This change with urinary products, for example Humegon and Normegon, to the recombinant FSH product, Puregon, required time and a transition period was, therefore, necessary.

Organon said that only 1% of infertile patients required both FSH and LH and for these patients it had ring-fenced its urinary gonadotrophin, Humegon, which was supplied to a doctor on request.

Organon noted that it had no control over what was published in the BNF and that the BNF might not reflect commercial availablility.

PANEL RULING

The Panel noted that Humegon and Normegon were still available even if supplies of these products were reserved for patients requiring both FSH and LH. The Panel considered that the situation regarding the supply of Humegon and Normegon should have been explained more clearly. In the Panel's view a statement saying that Humegon and Normegon were "no longer supplied" would give the impression that they were no longer available. This was not true. The Panel ruled a breach of Clause 7.2 of the Code.

4 The difference between Puregon and former fertility medicines

COMPLAINT

Serono said that the section comparing Puregon to former fertility medicines began with the statement "The basic active ingredient - FSH - is the same." This was incorrect because the older fertility products Normegon and Humegon, both currently available, contained FSH and LH as active ingredients. A breach of Clause 7.2 was alleged.

RESPONSE

Organon said that that section of the leaflet asked the question "So is Puregon different from former fertility drugs?" The answer sought to reassure patients that the principal active ingredient in their medicine was unchanged. The answer in the leaflet was primarily for the purpose of informing and reassuring women prescribed Puregon. There was no doubt that FSH was the predominant active component of urinary gonadotrophins and more recent urinary gonadotrophin formulations were developed to improve the purity of FSH. Extensive explanation and clarification that in some

urinary gonadotrophin preparations LH activity was also present would be inappropriate for this general infertility information leaflet. In practice only 1% of women treated with gonadotrophin required additional LH activity for obtaining adequate response.

PANEL RULING

The Panel noted that Puregon contained only FSH while the former fertility medicines contained a mixture of FSH and LH. The Panel noted Organon's submission that only 1% of women treated with gonadotrophin required additional LH activity for obtaining an adequate response. Almost all women only required FSH. The Panel considered that with the former fertility medicines the basis of therapy had been the FSH component in the vast majority of cases. In the Panel's view the statement that the basic active ingredient in Puregon was the same as that in the former fertility medicines was true. The statement did not mean that both Puregon and the older products contained only FSH but that FSH formed the basis of therapy in each. No breach of Clause 7.2 was ruled.

Complaint received 29 April 1997

Case completed 19 June 1997

CASE AUTH/536/4/97

NO BREACH OF THE CODE

GENERAL PRACTITIONER v ALLEN & HANBURYS

Promotion of Flixotide

A general practitioner complained about a mailing for Flixotide (fluticasone) issued by Allen & Hanburys. The complainant said that his understanding of the new British Thoracic Society (BTS) Guidelines was that fluticasone was twice as potent as budesonide but that the Turbohaler allowed a reduction of one half of the dose of medicine used. In the mailing Allen & Hanburys had compared the cost of Flixotide via an Accuhaler with approximately twice the dose of budesonide via a reservoir powder device (Turbohaler). It was alleged that this did not correlate with the BTS Guidelines and was misleading.

The Panel noted that the chart in the mailing was very clear as to the doses of fluticasone and budesonide being compared. The dose ratio for fluticasone:budesonide in mild asthma was 1:2, and in moderate and severe asthma 1:1.6. Given the clinical data and the equivocal nature of the BTS Guidelines regarding the dose of steroid via a Turbohaler, the Panel did not consider the dose ratios were unreasonable. The Panel considered that the chart was not misleading and ruled no breach of the Code.

A general practitioner complained about a mailing for Flixotide (fluticasone) issued by Allen & Hanburys (ref 20055047 - AP/April 1996). The one page chart was headed "A comparison of multi-dose powder devices" and gave the daily costs of controlling mild, moderate or severe asthma in adults with beclomethasone (Becodisks), budesonide from a reservoir powder device (Turbohaler) or Flixotide Accuhaler.

For patients with mild asthma the dose of budesonide was given as 200 micrograms, 1 puff bd, and the dose of Flixotide as 100 micrograms, 1 blister bd. In moderate asthma the doses were given as 400 micrograms, 1 puff bd, and 250 micrograms, 1 blister bd, respectively. In severe asthma the dose of budesonide was given as 400 micrograms, 2 puffs bd, and for Flixotide a dose of 500 micrograms, 1 blister bd, was given. The doses of Flixotide given for moderate asthma and for severe asthma were each followed by an asterisk. The explanation for the asterisk was given at the end of the dosage information as "nearest equivalent dose". According to the chart, Flixotide was the most expensive treatment for the control of both mild and moderate asthma in adults and budesonide from a reservoir powder device was the most expensive treatment of severe asthma in adults.

COMPLAINT

The complainant said that his understanding of the new British Thoracic Society (BTS) Guidelines was that fluticasone was twice as potent as budesonide but that the Turbohaler allowed a reduction of one half of the dose of medicine used.

In its chart Allen & Hanburys had compared the costs of Flixotide via an Accuhaler with approximately twice the dose of budesonide via a reservoir powder device (Turbohaler). The complainant said that this did not correlate with accepted (BTS) guidance and was misleading.

RESPONSE

Glaxo Wellcome said that the item referred to was prepared as a representative's leavepiece and had only ever been used as such. The comparisons all referred to the use of inhaled corticosteroids taken by multi-dose powder devices in the treatment of asthma in adults.

Glaxo Wellcome said that the new BTS Guidelines (The British Guidelines on Asthma Management - 1995 Review and Position Statement) were published as a supplement to "Thorax" in February 1997. As their title implied they represented a summary of the position agreed at a meeting at the end of June 1995. The Guidelines stated that fluticasone was "as effective as beclomethasone dipropionate and budesonide at half the dose when given by equivalent delivery systems". In support of this statement the Guidelines referred to four studies, three of which compared fluticasone with beclomethasone taken via either metered-dose inhalers or Diskhalers, and one study which compared fluticasone via the Diskhaler with budesonide via the Turbohaler. Copies of all of these studies were provided to confirm the Guidelines' statement. However, this statement also reflected the Flixotide data sheets which stated that "Equivalent disease

control is usually obtained at half the daily dose of other currently available inhaled steroids".

In a later paragraph of the Guidelines which addressed the systemic effects of inhaled corticosteroids was the statement "The Turbohaler delivers approximately twice as much inhaled steroid to the lung and doses should probably be halved when this device is used but, as in all cases, dosage should be titrated against control of asthma and treatment reduced when control is achieved". A copy of the paper which supported this statement was provided. Glaxo Wellcome pointed out that this study referred to lung deposition and not to clinical efficacy. The data sheet for Pulmicort (budesonide) Turbohaler stated "In keeping with medical practice, when transferring patients to Turbohaler from other devices treatment should be individualised and consideration given to the drug and the method of delivery".

While Glaxo Wellcome supported the use of the BTS Guidelines, it accepted the statement of the Coordinating Committee for the Guidelines which stated that a revision was needed in 1997/8 which would necessitate completely re-writing the Guidelines. Perhaps this ambiguity would be removed?

Glaxo Wellcome contended that there were further studies which supported the statement that fluticasone was at least as effective as budesonide at half the daily dose and these were studies comparing fluticasone taken via either a metered-dose inhaler, Diskhaler or Accuhaler with budesonide via the Turbohaler. The weight of evidence when comparing fluticasone in its dry powder inhalers, the Diskhaler and the Accuhaler, with budesonide in the Turbohaler was in favour of fluticasone. For example, in an 8 week study comparing patients treated with fluticasone Diskhaler 200 micrograms bd with patients treated with budesonide Turbohaler 400 micrograms bd there was a greater benefit for those patients receiving fluticasone both in terms of the faster rate of improvement in mean morning peak expiratory flow (PEF) in the first week and the increase in mean morning PEF over the whole study, compared with those receiving budesonide, in spite of fluticasone being used at half the daily dose of budesonide. Pickering *et al* showed equivalence in a 4 week study in 277 adult asthmatics, comparing fluticasone Accuhaler 250 micrograms bd with budesonide Turbohaler 600 micrograms bd, a dosage ratio of 1:2.4. In addition fluticasone had less suppressive effect on mean morning serum cortisol levels than budesonide.

A four week study in 321 children with asthma showed that fluticasone Accuhaler 100 micrograms bd was at least as clinically effective as budesonide Turbohaler 200 micrograms bd. In particular, there was a greater increase in mean percent predicted morning PEF in those children on fluticasone than in those on budesonide.

Finally, the study by Ringdal *et al*, showed a clear advantage in favour of fluticasone when fluticasone Diskhaler 400 micrograms bd was compared with budesonide Turbohaler 800 micrograms bd (1:2) over 12 weeks in a total of 518 patients with asthma. This advantage applied to a number of parameters; for example, mean morning PEF, mean evening PEF, diurnal PEF variation, mean percent (%) predicted PEF and clinic measurements of PEF, forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC). This efficacy advantage was associated with less effect on mean morning serum cortisol levels in those patients receiving fluticasone compared with those receiving budesonide.

Glaxo Wellcome submitted that the comparisons between the cost of Flixotide via the Accuhaler with approximately twice the dose of budesonide via the Turbohaler were justified and fair. Therefore the company believed that this promotional item was not in breach of the Code.

PANEL RULING

The Panel noted that the Flixotide data sheet stated that "Equivalent disease control is usually obtained at half the daily dose of other currently available inhaled steroids". The BTS Guidelines confirmed that if fluticasone and budesonide were administered via equivalent delivery systems then the dose ratio of each should be 1:2 respectively.

The Panel noted that the BTS Guidelines stated that the Turbohaler delivered "... approximately twice as much inhaled steroid to the lung and doses should probably be halved when this device is used but, as in all cases, dosage should be tritrated against control of asthma and treatment reduced when control was achieved". This section was referenced to a study by Thorsson which compared lung deposition from a Turbohaler with that from a pressurized metered dose inhaler.

The Panel noted that clinical data comparing fluticasone with budesonide via a Turbohaler showed that the ratio of doses, instead of being 1:1, as suggested by the Guidelines, was still in the region of 1:2. It appeared to the Panel that clinical data involving the budesonide Turbohaler did not support the results of the lung deposition study which had been carried out on healthy volunteers.

The Panel compared the licensed doses of budesonide administered via a metered dose inhaler with those of budesonide via a Turbohaler (Pulmicort - ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1996-97) and noted that the daily dosage for both products was similar. The adult dose of budesonide via a metered dose inhaler was 200 micrograms twice daily increasing to a daily dosage of 1600 micrograms if required for periods of severe asthma. For budesonide via a Turbohaler the adult dose was given as 200-1600 micrograms daily in divided doses when starting treatment, during periods of severe asthma and while reducing or discontinuing oral steroids. In adults with stable mild to moderate asthma a once daily dose of up to 800 micrograms was recommended.

The Panel noted that the chart was very clear as to the doses of fluticasone and budesonide being compared. The dose ratio for fluticasone:budesonide in mild asthma was 1:2, and in moderate and severe asthma 1:1.6. Given the clinical data, and the equivocal nature of the BTS Guidelines regarding the dose of steroid via a Turbohaler, the Panel did not consider that the dose ratios were unreasonable.

The Panel considered that the chart was not misleading and ruled no breach of Clause 7.2 of the Code.

Complaint received **29 April 1997**

Case completed **14 July 1997**

Case AUTH/537/5/97

PROFESSOR OF MEDICINE v CP PHARMACEUTICALS

Promotion of Hypurin

A professor of medicine complained about the phrase "who needs hypos?" which appeared in advertising for Hypurin issued by CP Pharmaceuticals. The complainant alleged that the phrase would imply to patients or healthcare professionals that the new insulin was not going to cause hypoglycaemia and was irresponsible and potentially dangerous.

The Panel noted that the materials were designed for healthcare professionals and not patients. The Panel considered that the layout and content of the material was such that there was an implication that Hypurin Bovine and Hypurin Porcine would provide control without the risk of hypoglycaemia or a reduced risk of hypoglycaemia. The Panel ruled that the page was misleading in breach of the Code.

COMPLAINT

A professor of diabetic medicine complained about the promotion of Hypurin by CP Pharmaceuticals Limited. Hypurin was animal insulin in cartridges for pen injection.

The complainant stressed that this was not a complaint about the product, which she welcomed, but about the use of an advertising slogan suggesting that this insulin would not produce hypoglycaemia in contrast to other insulins. The complainant had already registered her concerns with the company but said that the response received was facile and the complainant assumed from that that the company intended to take no action.

The complainant objected to the slogan "Who needs hypos?" written on the top of advertising material. This would imply to the patient that these animal insulin cartridges would provide glycaemic control in diabetes without risk of hypoglycaemia which was patently absurd.

The complainant said that the background to the advertising campaign must reside in the fact that CP Pharmaceuticals had developed the product in response to pressure from the diabetes community in general and the British Diabetic Association in particular, resulting in concerns that hypoglycaemia might be worse either in frequency or severity in patients who had converted to the use of human insulin. Like most clinical diabetologists, the complainant welcomed the introduction of the new product, because despite scientific evidence that human insulin did not influence hypoglycaemia, there was no doubt that a significant minority of patients were uncomfortable on it and to date had been prevented from using pen injection devices to administer insulin because such devices had only been available with human insulin. Clearly the new product would increase patient choice and was extremely desirable. However, to suggest to patients, or indeed healthcare professionals, that the new insulin was somehow magically not going to cause hypoglycaemia was irresponsible and potentially dangerous. Currently available insulins all carried significant risk of hypoglycaemia and a suggestion that one insulin was less prone to do this than another was totally unfounded and might create a complacency that could put patients' lives at risk.

RESPONSE

CP Pharmaceuticals said that the phrase "Who needs hypos?" to which the complainant objected appeared on an advertising brochure (Ref HP18), in journal advertisements (HP19 & HP23) and on exhibition panels.

At a meeting with CP Pharmaceuticals in January 1997, the British Diabetic Association (BDA) had the opportunity to comment on the proposed campaign slogan "Who needs hypos?". The only question raised was based on the possibility that this advertisement would be sent to, and potentially misconstrued by, patients. The BDA was assured that the campaign would be sent to professional healthcare workers only. On the basis of this assurance it was agreed that such professionals would understand the meaning of the headline and would not take it out of context.

The advertising brochure was distributed to consultant diabetologists, consultant physicians with an interest in diabetes, consultant geriatricians or paediatricians with an interest in diabetes, diabetic specialist nurses, principal pharmacists, and GPs with an interest in diabetes. Advertisements were placed in the Pharmaceutical Journal, 3 May 1997, Chemist & Druggist, 31 May 1997, and MIMS, May 1997. All the material was intended for healthcare professionals only. It was neither intended for, nor distributed to, patients.

CP Pharmaceuticals explained that there had been debate since 1987 over the question of hypoglycaemic attacks in patients following transfer from animal to human insulins. The situation was summarised in the latest Edition of Martindale "The Extra Pharmacopoeia", 1996,

"Some diabetic patients have experienced severe, sometimes fatal, hypoglycaemia after transfer from animal (especially bovine) insulin to human insulin. Also some patients have complained that after transfer they are less aware of the symptoms of a hypoglycaemic attack. Unfortunately studies investigating the risks from such a change-over have not been able to quantify the risks or even conclusively confirm them. Despite that, it is still prudent to be cautious at any change from animal insulin to human insulin and animal insulin should remain available.".

and in the current edition of the British National Formulary (BNF), March 1997,

"Some patients have reported loss of warning of hypoglycaemia after transfer to human insulin. Patients should be warned of this possibility and if they believe that human insulin is responsible for their loss of warning it is reasonable to transfer them back to porcine insulin.".

Although the evidence to date regarding any significant clinical difference between animal and human insulin remained inconclusive, there was a large cohort of patients who considered that there was a difference and in many cases it was the perceived loss of warning of hypoglycaemia which was the central issue.

Traditionally hypodermic syringes and needles had been used for the subcutaneous self-administration by patients of insulin provided in vials. More recently pen-injector devices had become available for the delivery of insulins provided in cartridges, but only for human insulins. This has meant that some patients for whom animal insulin was considered more suitable had had to continue to use hypodermic syringes and needles for self-administration. If they wished to use a pen device they had had to use a human insulin preparation. The frustration behind this lack of choice, together with the need for assurance that animal insulins would continue to be produced and the need for animal insulins in cartridge form, was graphically illustrated in the form of a 140,000 signature petition which was presented to CP and, as understood by the company, to Novo Nordisk, by the BDA in September 1994.

The objectives of the CP campaign for its new products were twofold. First it needed to announce clearly the arrival of the cartridges, reducing or even eliminating the need for hypodermic syringes or "hypos". Secondly it was important to remind healthcare professionals of the perceived loss of warning of hypoglycaemic attacks ("hypos") in some patients transferred from animal to human insulin. Whilst many clinicians were clearly *au fait* with this issue, the company knew that there were many circumstances where patient preference and choice had been limited by the unsubstantiated view that human insulin was clearly superior and/or the incorrect view that animal insulin was being withdrawn from the market.

To achieve the above objectives the company therefore intentionally made use of the two uses of the word "hypo" in the form of a thought-provoking rhetorical question. "Who needs hypos?". This was followed by the phrase "At last .... naturally derived bovine insulins in 1.5 ml cartridges" and by a photograph of a hand holding a cartridge, emphasising the replacement of the "hypo" by the cartridge and pen. In the advertising brochure this was followed by (on page 2) two quotes from the BNF, the first relating to the theoretical but unproven lower immunogenicity of human insulin, the second regarding loss of warning of hypoglycaemia in some patients transferred to human insulin. The second quote was chosen to provide a concise but balanced rationale for a transfer back to animal insulin in some cases. Had the company wanted to infer that these animal insulins would be less likely to produce hypoglycaemia than other (human) insulins it could have used any of a number of quotes from literature supporting that view, but such quotes would not have provided a balanced view according to current medical opinion and the company did not wish to convey such a suggestion.

CP submitted that the question "Who needs hypos?" was simply an eye-catching *double-entendre* alluding to the fact that hypodermic syringes might no longer be needed by patients on animal insulins, and to the problem of hypoglycaemia for diabetic patients, a distressing problem which they did not need and which had, at least in some quarters, been discounted in the belief that it was not a real problem for patients on human insulins.

The rhetorical question could not be construed as suggesting that these new insulins were not going to cause hypoglycaemia - such a suggestion would be absolute nonsense and no healthcare professional with any knowledge of insulin therapy could conceivably be so misled. Nor could this question be interpreted as suggesting that these insulins were less prone to cause hypoglycaemia than other insulins. Healthcare professionals in diabetes were well aware that hypoglycaemia was a potential hazard of any insulin and would never be persuaded to be complacent regarding that risk.

The only point that was made in the whole copy in relation to hypoglycaemia was the use of a balanced quotation from the BNF, providing a rationale for a transfer back to animal insulins in some cases, but making no claim or inference that hypoglycaemia would not then ever occur in such patients.

CP stated that three other complaints, all on the same theme, had been received from other healthcare professionals. The total of four represented 0.16% of the healthcare professionals who received this material in the mailing. A complaint had also been received from the BDA.

PANEL RULING

The Panel noted that the materials were designed for healthcare professionals and not patients. The complainant's comments regarding a patient's understanding of the promotional material were therefore not relevant.

The Panel did not accept CP's submission that healthcare professionals would understand the reference to "hypos" in the question "Who needs hypos?" as being a reference to hypodermic syringes. In the Panel's view readers would take the use of the term "hypos" to be a reference to hypoglycaemia.

The front page of the brochure was headed "Who needs hypos?" followed by a photograph of an orchestral conductor underneath which appeared the statement "At last naturally derived animal insulins in 1.5ml cartridges". Underneath this statement was a photograph of a hand holding a cartridge. The product names were given at the bottom of the page. The Panel considered that the layout and content of the page was such that there was an implication that Hypurin Bovine and Hypurin Porcine would provide control without the risk of hypoglycaemia or with a reduced risk of hypoglycaemia. The Panel considered that the page in question was misleading and therefore ruled a breach of Clause 7.2 of the Code. This ruling applied also to the journal advertisements and any other material which had the same layout.

Complaint received **1 May 1997**

Case completed **27 June 1997**

CASE AUTH/540/5/97 and AUTH/541/5/97

DIRECTOR/MEDIA v LAGAP and APPROVED PRESCRIPTION SERVICES

Gifts and inducements

An article in The Sunday Times of 4 May criticised promotional schemes run by Lagap and Approved Prescription Services. Lagap was alleged to have recently introduced a promotion of Sainsbury's vouchers to run alongside existing offers of vouchers for Marks & Spencer and Dixons. Another Lagap scheme offered Air Miles from British Airways. In relation to Approved Prescription Services, it was alleged that pharmacists buying certain products were given vouchers which could be exchanged for foreign holidays or electrical goods. In accordance with established practice, these allegations were taken up as complaints under the Code.

The Panel noted that the provision of gift vouchers and gifts was subject to the Code. This was not a matter relating to prices, margins and discounts which were exempt from the Code. None of the schemes had been offered to doctors but they had been available to pharmacists who were health professionals. The Panel ruled each company to have been in breach of the Code because the offer of gifts and inducements to health professionals in connection with the promotion of medicines was not permissible.

The Panel appreciated that the companies had considered that their schemes were acceptable and was pleased to note that they had suspended them pending final resolution of the matter.

These cases arose from an article in The Sunday Times, 4 May 1997, headed "Drug firms face probe over gifts for doctors". In accordance with established practice, the criticisms in the article were taken up as complaints under the Code of Practice. Initial consideration was given to the cases in May but it was decided to defer making rulings pending developments elsewhere. The companies were suspending the schemes and the legal position remained uncertain. The cases were finally considered in July by which time the legal position had become clearer.

Case AUTH/540/5/97: Lagap Pharmaceuticals Ltd

COMPLAINT

Reference was made in the article in The Sunday Times to Lagap which was quoted as having said that it had recently introduced a promotion with Sainsbury's vouchers to run alongside existing offers of vouchers from Marks & Spencer and Dixons. Another Lagap scheme offered Air Miles from British Airways.

Lagap Pharmaceuticals Ltd had advised the Authority on 23 May that it was ceasing the use of promotional activities such as Marks & Spencer vouchers from July 1997 onwards.

RESPONSE

Lagap pointed out that it did not undertake any promotional activity to doctors. All of its promotion was directed to community pharmacies and wholesalers.

Lagap said that its major schemes, namely Marks & Spencer vouchers and Air Miles, started prior to 1 January, 1993. They were clearly alternative forms of discount since the pharmacist could either purchase goods at lower prices without receiving "vouchers" or purchase goods at higher invoice prices plus "vouchers". They were not presents or gifts, they were definite alternatives to cash discounts.
Sainsbury's/Currys/Dixons vouchers had been introduced simply to provide an alternative to Marks & Spencer vouchers.

In this context, Lagap concluded that sections 24 and 25 of counsel's opinion taken by the ABPI were highly relevant since they clearly confirmed that Clause 18.1 of the Code was perfectly explicable when applied to promotion to doctors but "slightly less clear" when applied to gifts to pharmacists. Lagap contended that its Air Miles/Marks & Spencer schemes had never been gifts but clear alternatives to discounts as frequently practised by companies marketing over-the-counter (OTC) products to pharmacists. The clear difference was that for such OTC products, unlike generic medicines, they had the ability to influence the choice of medication - an interesting topic for future discussion.

In terms of these two well-established schemes, which were in existence at Lagap and other companies since the early 1990s, there had never been any remote possibility, as implied by the original The Sunday Times article, that such schemes could influence the choice of a prescribed medicine. Counsel's comments reinforced his clear understanding of this last fact:

"The aim of the prohibition is slightly less clear when applied to gifts to pharmacists to persuade them to buy POMs. For these can only be supplied to a patient on prescription by a doctor and all products available to a pharmacist must have been the subject of a marketing authorisation and must therefore be considered safe, effective and of good quality."

An immediate clarification of the current grey area of interpretation was essential since the guidelines were clearly focused on "gifts/promotional schemes" directed at prescribers and were totally inappropriate where dispensers were considered. Lagap was reviewing the situation. Lagap wished to be actively involved with other generic colleagues in this process.

To conclude, despite the admitted difficulties of interpretation referred to above, Lagap was now aware of the Appeal Board's final ruling in connection with Marks & Spencer vouchers. Although it questioned the validity, or objective basis of the judgement, it would abide by a decision taken in good faith.

In a letter dated 30 June 1997, Lagap reconfirmed the information previously given. From 1 July 1997, Lagap would cease to use its Marks & Spencer voucher

promotional scheme and other similar voucher schemes. In relation to its Air Miles scheme, it would only meet its existing contractual obligations to various parties which ran out in October 1997. It undertook that the Air Miles scheme would be terminated as soon as legally permissible.

Lagap added the caveat that the cancellation of such schemes was based on the assumption that any ABPI or other review confirmed that their usage was not legal. If this was not the case, then Lagap reserved the right to restart such schemes.

Case AUTH/541/5/97: Approved Prescription Services Limited

COMPLAINT

The article in The Sunday Times stated that pharmacists buying certain products from APS were given vouchers which could be exchanged for foreign holidays or electrical goods.

Approved Prescription Services Limited (APS) advised the Authority on 16 May that the scheme had been suspended until the position was resolved.

RESPONSE

APS said that it offered a range of some 500 commodity generic products. The bulk of the company's sales were to retail pharmacists. APS products were unbranded in the sense that they were used by pharmacists to fill the 55% of prescriptions that were written generically. Generic products were multi-sourced, ie they were identical products which were available from a variety of different manufacturers. Pharmacists were reimbursed by reference to the Drug Tariff. There was no price regulation in the market and pharmacists sought and expected to receive discounts. The discounts and the means by which they were offered were, and always had been, a means of competition between suppliers. Discounts came in a variety of forms: discount off invoice, free of charge stock and, in the case of APS to some customers, voucher exchange points. APS did not offer doctors the voucher exchange, or any equivalent, scheme. Various means of offering discounts were widespread in the generics industry and were necessary to compete in a commodity business.

APS submitted that voucher exchange was introduced in September 1991 as a means of engendering loyalty to APS and to retain purchasers from one order to the next. Voucher exchange had always been an alternative discount. Some customers rejected the concept and instead required lowest net price. The cash value of voucher exchange was generally in the range of 2-15% discount off list for customers who participated supplemented by other discounts of the types described above. Voucher exchange points were issued to the business or company which ordered, received and paid for products and not to individuals. Points were allocated on a computer system and a statement indicating points available for redemption was issued to all relevant customers monthly. A bi-annual catalogue for voucher exchange was published and was mailed to all current voucher exchange customers, of which there were approximately 800. A copy was provided. Foreign holidays did not feature in the current brochure.

APS products were sold by representatives as "baskets", attempting to cover as broad a range of a customer's requirements as possible. APS was in the business of satisfying demand, not generating it. The company could only supply to fill demand from pharmacists arising as a result of open generic prescriptions from doctors. Neither the company nor pharmacists had any influence on the product received by the patient. No aspect of APS's trading practices influenced the actual product, strength or dosage form that the patient received.

APS stated that generic companies competed with each other to supply the same products. The supply of voucher exchange points was purely a business matter and raised no ethical issues for APS (unlike in the branded sector where drug companies competed to persuade doctors to prescribe their own products and so influenced the medicine received by a patient). Voucher exchange points were available regardless of the generic products ordered (ie they were not product specific).

APS had never believed and, indeed, the ABPI had never advised it, that its scheme breached Regulation 21(1) of The Medicines (Advertising) Regulations 1994. In any event, APS's scheme appeared to be exempted from Regulation 21(1) because of Regulation 21(4), which said:

"Nothing in this Regulation shall affect measures or trade practices relating to prices, margins or discounts which were in existence on 1st January 1993."

APS had always regarded voucher exchange as a legitimate form of discounting and it had been an established part of its trading practice since 1991. Its other discounts referred to above had been offered for many years and in any case prior to 1993. The scheme was detailed by company representatives and was well known. The full scheme was explained to the Director and Secretary of the Authority at a meeting in July 1996 and the brochure and means of operation left with them. APS had received no complaints throughout the entire history of the scheme until the press raised the issue recently.

APS was made aware at the July 1996 meeting, referred to above, of the forthcoming ABPI working party to review Clause 18 of the Code of Practice and had been awaiting an outcome. If the review had indicated that APS's voucher exchange scheme was incompatible with the Code, then it would have withdrawn it. APS had no wish to be, nor to be held to be, in breach of Regulation 21(1). Following the article in The Sunday Times and subsequent enquiries from the ABPI and the MCA, APS had taken the decision to temporarily suspend the voucher exchange scheme with effect from 8 May. As the Authority knew, the article implied that promotional schemes such as this influenced the medication received by patients. This was clearly not the case. However, until APS had had the opportunity to make this clear to the ABPI and the MCA, the scheme had been suspended so that these authorities were 100% comfortable with APS trading practices.

APS had already responded to the MCA on this matter and had invited the MCA to meet with it to agree a resolution. Pending this resolution, the scheme would remain suspended.

APS formally advised the Authority on 27 June that the APS Berk Voucher Exchange Scheme, which had been suspended following the Authority's enquiry, had now been terminated.

Cases AUTH/540/5/97 & AUTH/541/5/97

PANEL RULINGS

The Panel noted that attention had first been drawn to the question of gifts and inducements given in relation to the purchase of medicines in Case AUTH/421/4/96 which involved the provision of mountain bikes and Marks & Spencer gift vouchers in exchange for orders from pharmacies for medicines. The company concerned in that case had ended its participation in the scheme but had declined to give the requisite undertaking and assurance as to future activities and had in fact left the ABPI rather than do so.

That case had given rise to some dissent as there were those who took the view that the decision was wrong, maintaining that gifts of mountain bikes and the like were a form of discount and thus exempt from the requirements of both the Code and the relevant legislation. That had not been the view of the Panel which had ruled a breach of Clause 18 and nor of the Code of Practice Appeal Board which, upon appeal, had agreed with the Panel's ruling. The Appeal Board said that discounts, margins and prices, which were excluded from the provisions of the Code, were financial terms that did not extend to mountain bikes and the like.

Aware that there were other similar schemes in operation, the Appeal Board asked the Authority to draw the outcome of Case AUTH/421/4/96 to the attention of the companies concerned. That had been done in June 1996 but no further action was taken at that time.

Because of the possible ramifications of the decision in Case AUTH/421/4/96, the ABPI subsequently took leading counsel's opinion on the outcome. Counsel expressed the view that the decision had been the correct one, though he commented that the relevant provision of the Code was somewhat obscure. The ABPI Board of Management had asked the Authority to set up a working party to look at the relevant clause of the Code, Clause 18, to see whether it needed to be amended or to be made the subject of a more detailed explanation.

The outcome in Case AUTH/421/4/96 had been notified to the Medicines Control Agency which had also been provided with a copy of the opinion obtained by the ABPI. The Authority was aware as a result of discussions with MCA officials that the MCA was concerned about the question of gifts and inducements and was itself taking counsel's opinion on the interpretation of the regulations.

The working party set up by the Authority had considered that the outcome in Case AUTH/421/4/96 was reasonable in the light of the legal position though it considered that more guidance could be given once the MCA had clarified the legal position. Subsequently, the ABPI decided to propose to its members that the supplementary information to Clause 18 be augmented to clarify the position and the MCA came out with a firm declaration that gifts and inducements given to obtain orders were totally unacceptable by means of a letter issued in July 1997.

The Panel noted that the Authority had been placed in a difficult position in the matter. The Appeal Board had asked the Authority to notify other companies with schemes of the outcome of Case AUTH/421/4/96 and that had been done. It had not asked that further action be taken. The Authority had decided not to pursue those companies operating schemes until the legal position was definitively resolved as the ending of an ongoing scheme had significant commercial implications. It was of far more consequence than, for example, having to cease the use of a particular advertisement or claim.

The article in The Sunday Times on 4 May 1997 had obliged the Authority to take its criticisms up with Lagap and APS as the Authority was duty bound to take up such matters. The Panel had, however, deferred making a ruling until now. The legal position had still been uncertain at the time and both companies had indicated that they were suspending the schemes in question.

The Panel considered that it was now in a position to make rulings on the matters raised in The Sunday Times. The provision of gift vouchers and gifts was not a matter relating to prices, margins or discounts and the schemes were thus not exempt from the provisions of the Code. The Panel considered that neither the Lagap schemes relating to vouchers and Air Miles nor the APS Berk Voucher Exchange Scheme were acceptable and ruled each company to have breached Clause 18.1 of the Code which prohibits gifts and inducements to health professionals in connection with the promotion of medicines.

The Panel noted that neither scheme had been offered to doctors. The Lagap schemes had been available to pharmacists and wholesalers. The APS scheme had been available to pharmacists. Clause 18.1 of the Code applied to health professionals which included pharmacists.

The Panel was pleased to record that the schemes in question were now being brought to an end. It appreciated that each of the companies had been placed in an awkward position. They had genuinely believed their schemes to be acceptable and had suspended them when they were convinced that that was not so.

Proceedings commenced **7 May 1997**

Cases completed

Case AUTH/540/5/97 **1 September 1997**

Case AUTH/541/5/97 **15 August 1997**

CONSULTANT PSYCHIATRIST v JANSSEN-CILAG and ORGANON

Internet site

A consultant psychiatrist complained about an Internet site run by Janssen-Cilag and Organon. It was alleged that the site was being promoted widely in Internet newsgroups. The site had minimal information about schizophrenia and was designed and controlled with a view to marketing risperidone (Risperdal). In the complainant's view it was disguised promotion addressed to the general public.

The Panel noted that the site was on a Belgian server. It was in English but it was inevitable that most medically orientated sites would be in English as it was the internationally recognised scientific language. Only those sections offering general information were available to the general public. Physician only sections were fully password protected and no specific UK information was included. Neither Janssen-Cilag nor Organon in the UK had added information and neither had promoted the existence of the site. The Panel considered that the UK companies were sufficiently removed from the Internet site for it not to be considered promotion to the general public on their behalf. The Panel did not accept that the site constituted disguised promotion as alleged. The Panel therefore ruled no breach of the Code.

COMPLAINT

A consultant psychiatrist complained about an Internet site wholly created, promoted, run and funded by Janssen-Cilag Ltd and Organon Laboratories Limited.

The complainant said that the site was freely available to all-comers on the Internet and was being promoted widely to all and sundry in Internet newsgroups. The complainant provided an example of a notice posted on such a newsgroup on 30 April 1997 by an employee of Janssen-Cilag. The notice did not make the sponsored nature of this new 'resource' plain enough. The note was unsigned, but was placed by a Janssen employee in a newsgroup open to all.

The complainant said that the resource in question, Futurcom, really had minimal information about schizophrenia and was designed and controlled with a view to marketing risperidone (Risperdal - Janssen-Cilag's product) which was heavily featured in a section of the website called Webtrack.

The complaint was based on the 'disguised' nature of this drug promotion by a Janssen employee through a public newsgroup, and through an Internet website accessible to all. In the complainant's view, the Code of Practice Authority needed to take immediate action to stop this kind of disguised promotional activity to the general public.

RESPONSE

Janssen-Cilag responded on behalf of both companies. Janssen-Cilag pointed out that the site should be viewed as a publication sourced in Belgium. It specifically said so in the disclaimer section for the site and elsewhere. The company submitted that as this information (both the site and the newsgroup posting) was placed on the Internet in Belgium and the information contained in it did not refer specifically to the UK use of any product, then it was outside the scope of the UK Code of Practice as outlined in the May 1996 edition of the Code of Practice Review on this subject.

Further, the company argued that no *prima facie* case had been established.

Janssen-Cilag provided a document giving details about the site.

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On the information supplied, the Director of the Authority ruled that there was no *prima facie* breach of the Code. The reasons for this decision were that the material was placed on the Internet in Belgium and did not specifically refer to the UK use of the product. Local Janssen-Cilag operating companies could provide information to their local psychiatrists on the section "Your Country" but currently only Belgium and Germany had posted information in this section. The UK had not. The section was password protected.

The complainant did not accept the Director's view that there had been no *prima facie* breach of the Code and made further comments.

The complainant asked the Authority to consider the following hypothetical example and wondered whether it would agree that there was a *prima facie* case:

A multinational pharma company sponsored a publication written in English, by a UK company, typeset in the UK, but printed in a foreign country then distributed to all-comers, including UK patients who approached their doctor with information from the publication.

The complainant assumed that this scenario was one in which the Authority would act.

The complainant then considered the Janssen Futurcom site which was sited on a Belgian server, possibly intentionally to avoid the Authority's interest. The site could be considered a sponsored publication as in the scenario above. It was almost fully published in English, not in Flemish or Walloon, and therefore could not be designed for a purely Belgian audience. Furthermore, the content was sourced from a medical communications company based in the UK and 'typeset' by another UK firm.

The complainant said that the site was freely available to be read by UK patients, the UK public and the UK medical profession.

What was not disclosed by Janssen-Cilag was the pure marketing intent of the site. The complainant explained

his point by referring to the HTML coding of the site which had key pointers to its intent. The hidden coding was as follows:

<META NAME="KeyWords" CONTENT="Risperdal, risperidone, schizophrenia, schizophrenic, mental, health, psychosis, psychoses, antipsychotic, Futurcom, Futurum, Futuris, Haldol, haloperidol, Webtrack, positive symptoms, negative symptoms, Janssen-Cilag, Janssen Pharmaceutica, www.futur.com, neuroleptic">

This coding revealed one of the key intentions, that people searching the Internet for keywords such as Risperdal (the UK trade name) or risperidone, Haldol or haloperidol were drawn to this site.

Given the site's sponsored nature and the strict control that Janssen-Cilag had had with regard to the marketing intent, the complainant considered that the Authority must ask in what way was the site sponsored by an 'unrestricted educational grant' as the pages stated.

The complainant could see little difference between the first scenario and the second. In the first scenario the complainant considered that the Authority would take action, but would it in the second? If the Authority did not, then the route was available to all pharmaceutical companies to publish freely on the Internet, as long as the server was based in an area not covered by bodies such as the Authority.

The complainant said that if the Authority failed to act in this case, he considered that it would have been misled and have lost sight of an important principle, and furthermore lost control over those it sought to regulate.

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As the complainant had not accepted the Director's view that there was no *prima facie* breach of the Code, the matter was referred to the Chairman of the Code of Practice Appeal Board in accordance with Paragraph 6.1 of the Constitution and Procedure for the Prescription Medicines Code of Practice Authority. The Chairman decided that the matter should proceed as a complaint.

The complainant's further comments were sent to Janssen-Cilag and Organon.

FURTHER RESPONSE

Janssen-Cilag again responded on behalf of both companies. Janssen-Cilag reiterated that the Futurcom website was a Belgian site, the information contained in it did not refer specifically to the UK use of any product, and hence, as per the Code of Practice's guidelines for "The Internet and the Code of Practice for the [UK] Pharmaceutical Industry", it was convinced that this website was outside the scope of the UK Code.

Janssen-Cilag said that the complainant hinted that the companies might purposefully have chosen to put this site on a Belgian server, to evade ABPI jurisdiction. The rationale for the Belgian server was much more straightforward. Janssen-Cilag's parent company currently had two Internet servers, one in the United States and one in Belgium. It was company policy that all sites preferentially be hosted on one of these servers. There was therefore no "possibly intentional" shift of the site to a location to "avoid the interest of the ABPI".

Janssen-Cilag UK had not been involved in the selection process of the server location.

Janssen-Cilag said that the complainant further pointed to UK companies' involvement in the production of the website and its English language. The fact that UK companies were involved in Futurcom was purely coincidental and based on practical considerations. Indeed, one of the medical communications companies involved had been managing most of the Belgium-based Janssen Pharmaceutica Strategic Marketing's "off-line" international communications for the psychiatry franchise for some time. To further underscore this point, Janssen Strategic Marketing in Beerse, Belgium, was currently working with Belgian, Canadian and German companies in the production of websites. Finally, English was well accepted as the scientific lingua franca and it was the dominant language on the Internet.

Janssen-Cilag submitted that another argument for this complaint being ruled out of the scope of the UK Code was that Janssen-Cilag UK and Organon UK had not promoted the existence of this website to a UK audience either through the Internet or by a paper-based communication or by word of mouth.

With regard to the complainant's hypothetical example, this was misleading since the example turned on the phrase "distributed to all-comers, including UK/patients...". Janssen-Cilag contended that a website was not "distributed". It existed in cyberspace and must be requested by the receiver. Neither Janssen-Cilag nor Organon in Belgium had distributed Futurcom but anyone with the appropriate equipment could request sight of the publicly available portion of this website.

To further demonstrate the invalidity of the complainant's hypothesis, Janssen-Cilag said that, as matters currently stood, a UK company could print an article in English on paper in the UK and could distribute it in a foreign country with material that did not comply with the UK Code if no copies of the article were distributed in the UK and the article complied with the other country's local requirements. If in this hypothetical situation, a UK member of the public journeyed from the UK to the foreign country and collected the paper copy and returned to the UK, the company had not breached the UK Code of Practice.

In conclusion, Janssen-Cilag contended that this complaint did not fall within the scope of the UK Code of Practice.

PANEL RULING

The Panel noted that the Internet site had been placed on a Belgian server for reasons of company administration. The site had been developed by Janssen-Cilag in Belgium. Janssen-Cilag in the UK had had no influence over the selection of the server site.

The Panel noted that the site was in English but considered that as the accepted international scientific language was English it was inevitable that most medically orientated sites would be in English and that as a natural consequence UK publishing/communications companies might be involved in their production. The Panel noted that one of the UK communications companies involved in the site was already working for

Janssen-Cilag in Belgium.

The Panel considered that the general public could already access information on medicines via public libraries. In addition more information was available on the Internet from both reliable and unreliable sources. With both libraries and the Internet, members of the public had to seek out the information they wanted. It was not sent to them. The Panel noted the submission from Janssen-Cilag that Futurcom in Psychiatry had a number of sections, but only those offering general information were freely available. Physician only sections were fully password protected and no UK specific information was included on the site. Neither Janssen-Cilag nor Organon in the UK had added information to the "Your Country" section. Neither of the two companies had promoted the existence of the site.

The Panel considered that the UK companies, Janssen-Cilag and Organon, were sufficiently removed from the Internet site for it not to be considered promotion to the general public on their behalf. The Panel did not accept that the site constituted disguised promotion as alleged. The Panel noted that the example of a notice posted by the employee of Janssen-Cilag Ltd, provided by the complainant, stated that "Janssen-Cilag and Organon are pleased to announce the launch of Futurcom in Psychiatry". The Panel therefore ruled no breach of the Code.

Complaint received **9 May 1997**

Cases completed **1 September 1997**

CASE AUTH/545/5/97

LILLY v SMITHKLINE BEECHAM

Seroxat leavepiece

Following a change in the Prozac product licence Lilly complained that a Seroxat leavepiece issued by SmithKline Beecham was no longer accurate in its comparison of the two medicines. SmithKline Beecham had agreed with Lilly and offered to withdraw the item but four months later it was still being used.

The Panel noted that the change in the Prozac product licence meant that both it and Seroxat were licensed for use in anxiety associated with depression and to claim that there was a difference between the two medicines in this regard was misleading. SmithKline Beecham had told its representatives to stop using the leavepiece but one had continued to do so. A breach of the Code was ruled.

Lilly Industries Limited complained about a Seroxat (paroxetine) leavepiece (0796ST : LP/6/048) issued by SmithKline Beecham Pharmaceuticals. The leavepiece was entitled "Seroxat and *fluoxetine* are not the same". The page at issue was headed "Seroxat - compare the difference", followed by four stab points the first of which was "Effectively relieves anxiety associated with depression".

COMPLAINT

Following a change in the Prozac (fluoxetine) licence in October 1996 to include anxiety associated with depression, Lilly had written to SmithKline Beecham in December 1996 to notify it of the change and allow the company to alter its promotional material which referred to the prior difference in the licensed indications of fluoxetine and Seroxat. In December 1996, SmithKline Beecham agreed that the leavepiece was no longer accurate and offered to withdraw it from use. Subsequent continued use of the leavepiece by representatives over two months was drawn to SmithKline Beecham's attention in March 1997. Lilly said that it was surprised and disappointed to have found the item being used at a meeting in April 1997.

Lilly alleged that the leavepiece was in breach of Clause 7.2 of the Code.

RESPONSE

SmithKline Beecham said that it had been in discussion with Lilly on a number of occasions with regard to the leavepiece, and agreement had been reached.

SmithKline Beecham said that all materials were removed from the field, and signed confirmations received from all representatives. It appeared, however, that in this instance there had been an error by a particular representative who had failed to destroy these items which he had stored with many other pieces in a box he used for such meetings. The representative in question had been warned that any such future omission would lead to disciplinary action and all members of the field force had been reminded of their responsibility in this regard.

SmithKline Beecham said that every effort would be made to ensure that such an error did not happen again.

PANEL RULING

The Panel noted that Prozac was recently licensed for use in anxiety associated with depression. To claim that there was a difference between the two medicines in their use in anxiety associated with depression was misleading, in breach of the Code. The Panel noted that SmithKline Beecham had instructed its representatives to withdraw the leavepiece but that it had been continued to be used by one of its representatives for whom it must take responsibility. A breach of Clause 7.2 was ruled.

Complaint received **9 May 1997**

Case completed **23 June 1997**

CASE AUTH/546/5/97

WYETH v ASTRA

Journal inserts on peptic ulcer disease

Wyeth complained about two inserts on peptic ulcer disease which had been in consecutive issues of Pulse. They had been supported by an educational grant from Astra. Wyeth said that the first contained an inaccurate price comparison which disadvantaged a regimen including lansoprazole (Wyeth's product) as compared to a regimen including omeprazole (Astra's product). Wyeth said that the second insert was promotional but it did not include prescribing information and its size exceeded that allowed. Both of the inserts were alleged to be disguised advertising.

Having examined the content of the inserts and noted the fact that they had been used by Astra's representatives, the Panel decided that both inserts were subject to the Code. Parts 1 and 2 were each ruled to breach the Code as they were disguised promotion and lacked prescribing information. Part 1 was also in breach because of the misleading price comparison.

The case concerned two inserts which had been in consecutive issues of Pulse, 15 and 22 February 1997. One was entitled "Peptic ulcer disease part 1. Evaluating the role of H. pylori" and the other "Peptic ulcer disease part 2. Organising care in practice".

It was stated in the inserts that they had been supported by an educational grant from Astra Pharmaceuticals.

COMPLAINT

Wyeth Laboratories alleged that the insert "Peptic ulcer disease part 1" contained misleading and inaccurate information on page 12 in the table entitled "Recommended triple therapy regimens". The table showed the costs of the regimen LCM (lansoprazole, clarithromycin and metronidazole) to be more expensive than OCM (omeprazole, clarithromycin and metronidazole).

The insert gave the cost of OCM as £29.59 and the cost of LCM as £30.01.

MIMS April 1997 showed that a 7 day pack of omeprazole 40mg (once daily) cost £17.72 and a 7 day pack of lansoprazole 30mg (twice daily) cost £16.68.

Therefore, since the antibiotic components of the OCM / LCM regimens were identical, the LCM regimen was less expensive by £1.04, not more expensive by £0.42 as stated in the insert.

The price of lansoprazole had been reduced on 1 August, 1996.

With regard to "Peptic ulcer disease part 2" there were more serious concerns. The insert was obviously promotional but did not carry prescribing information and was therefore in breach of Clause 4.1. Even if the article did carry the prescribing information as required by Clause 4.1 of the Code of Practice, the size of the article exceeded the guidelines laid down.

Throughout the insert "Peptic ulcer disease part 2" the only regimens described were those containing omeprazole whereas several other products and regimens were licensed for the treatment of *Helicobacter pylori.*

Wyeth's most serious concern related to the patient information sheet at the back entitled "What are the facts?". It was obvious from the style of the presentation that these sheets were meant to be reproduced and used for distribution to patients and once again were specifically tailored for omeprazole only containing regimens. This could well be construed as direct advertising to the public.

In summary, Wyeth believed that the two inserts represented disguised advertising and therefore were in breach of 10.1. If they were accepted by Astra as being advertising, then they failed to comply with the Code in terms of carrying the prescribing information as required by Clause 4 of the Code and their number of pages exceeded those allowed for this sort of advertising.

RESPONSE

Astra Pharmaceuticals Ltd responded to the points in turn.

1 The price comparison During 1996, Wyeth reduced the price of lansoprazole and unfortunately Astra and Pulse did not notice that the reduced price of lansoprazole was not included in the calculation. A letter from Pulse to this effect was supplied. This was a mistake and Astra apologised for it. If Wyeth had written to Astra on this matter, Astra would have acknowledged its error.

2 Promotional nature of the supplements and the need for prescribing information Considering the nature of inserts 1 and 2, they were not intended to be promotional. The articles were independently written and the inserts were independently produced, supported by an educational grant from Astra Pharmaceuticals Ltd. This was clearly stated on the first page. Given this, Astra did not believe that prescribing information was required.

3 Selective use of regimens Importantly, the supplements were clearly labelled part 1 and part 2 and needed to be considered together.

In part 1 specific attention was drawn to other regimens combining proton pump inhibitors with antibiotics, and lansoprazole was referred to by name (part 1, page 13, subheading - Triple Therapy), "A combination of a proton pump inhibitor with two antibiotics, usually for one week is the recommended regimen. All the regimens, therefore, contain either omeprazole or lansoprazole ....."

Part 2 specifically referred readers back to part 1 (part 2, page 6, Peptic ulcer management). "The key considerations in the management of peptic ulcer disease and *H.pylori* eradication therapy have been discussed in more detail in Part one...".

In the next paragraph, reference was made to omeprazole (O) amoxycillin (A) and metronidazole (M) "One of the

current recommended triple therapies ....". It was not stated to be the only one (part 2, page 6, subheading "Eradication therapy").

In part 2 of the supplement the OAM regimen was referred to because the supplement was based on the Suffolk Consensus Group Dyspepsia and Audit Guidelines, 1996. This was clearly stated on the contents page and again on page 9. This group used OAM (part 2, page 9) and so the specific reference made to this regimen in the context of the Suffolk Guidelines was both necessary and accurate.

4 Patient Information Sheet "What are the facts?" The first paragraph of this sheet was "These medicines have been prescribed by your doctor ....". It was clearly for use after OAM had been prescribed. The sheet was again based on the Suffolk Consensus, using their regimen. The sheet was therefore factual.

Therefore, Astra believed that the supplements sponsored by Astra were educational in the same way as other educational supplements produced by the medical press and did not believe that Clauses 4.1 or 10.1 of the Code had been breached.

Following a request for further information, Astra made two additional points.

5 The relationship between Astra Pharmaceuticals Ltd and the publishers Astra did not have any input into the preparation of the inserts. They were written by independent physicians. Astra did have an opportunity to see the inserts but it was not able to influence their content. The inserts were checked for compliance with the ABPI Code and errors were corrected, but Astra had no editorial input.

6 Use of the inserts Astra did receive copies for its own use. Representatives did have access to copies.

PANEL RULING

The Panel first had to decide whether the inserts (or either one of them) were subject to the Code. The inserts were sponsored by a company with a product interest in the therapeutic area involved and were thus potentially subject to the Code. No brand names were used in the inserts. The inserts had been used by Astra's sales representatives.

Part 1 referred to a number of regimens without particularly featuring on any one of them and the authors commented at the end that the perfect eradication regimen had not yet been found. The price comparison was out of date and inaccurate at the time that the insert was used and this prejudiced the interests of Wyeth. A further factor was that the insert had been made available to Astra's representatives. In the circumstances, the Panel considered that the insert had to be regarded as coming within the scope of the Code. It was ruled that the insert breached Clause 4.1 because of the absence of prescribing information for Losec, Clause 7.2 because of the inaccurate price comparison and Clause 10.1 as being disguised sales promotion.

Part 2 was based on the Suffolk Guidelines and so featured the use of a triple regimen using omeprazole (Astra's product Losec) rather than lansoprazole (Wyeth's product Zoton). The patient information leaflet was suitable only for patients given the regimen containing omeprazole. There were no leaflets for other therapies and no instructions as to the use of the leaflet. Astra's sponsorship of the insert and its enclosures meant, in the Panel's view, that it had to be regarded as being subject to the Code as promotion for omeprazole. A breach of Clause 4.1 of the Code was ruled because of the absence of prescribing information for omeprazole (Losec). The insert was also ruled to be in breach of Clause 10.1 of the Code as being disguised sales promotion.

There were no limitations on the size of this type of insert and no breach was ruled in that regard. The supplementary information to Clause 6.4 indicated that inserts and supplements which were not advertisements as such, though they might be regarded as promotional material, were not subject to the restrictions on the number of pages set out in Clauses 6.3 and 6.4.

Complaint received **12 May 1997**

Case completed **17 July 1997**

CASE AUTH/547/5/97

WYETH v KNOLL

Promotion of Protium

Wyeth made two allegations about the promotion of Protium by Knoll.

The claim "Precise control in acid-related disorders" was used extensively by Knoll. An asterisk by the claim was explained in small type beneath the claim as "Reflux oesophagitis, duodenal ulcer and benign gastric ulcer". Wyeth alleged that the casual reader would not notice this explanation and would be misled. The Panel considered that the immediate impression given was that Protium was licensed for use in all acid related disorders and this was not so. A breach of the Code was ruled.

A product summary booklet contained a table headed "Interactions listed on data sheets/SmPCs" in which there was the statement "Bioavailability of lansoprazole reduced" in relation to lansoprazole and antacids. Wyeth alleged that this was misleading and disparaging as the Zoton (lansoprazole) data sheet said that antacids might reduce lansoprazole bioavailability if taken within one hour of Zoton ingestion. The Panel considered that the statement was not sufficiently clear as it did not convey the fact that, given at least one hour apart, there was no interaction between Zoton and antacids. The statement did not accurately reflect the position and a breach was ruled. This was upheld upon appeal by Knoll.

Wyeth Laboratories complained about the promotion of Protium by Knoll Limited.

1 Claim "Precise control in acid-related disorders"

COMPLAINT

Wyeth drew attention to the above claim which was repeated extensively in advertising materials, detail aids and leavepieces. Wyeth provided a journal advertisement (ref ETH:2273b/8/96). The claim was obviously broad in scope and related to claims far in excess of those granted by the product authorization. An asterisk usually appeared beside the claim. The explanation for the asterisk was given in small type beneath the claim as "Reflux oesophagitis, duodenal ulcer and benign gastric ulcer". Wyeth alleged that this was a deliberate attempt to mislead and appear to have a broad licence of claims and duration of therapy as it was highly unlikely that casual readers would read the explanation for the asterisk which was given in small type. Wyeth alleged the claim was in breach of Clause 7.2 of the Code.

RESPONSE

Knoll submitted that the product licence for Protium used the actual words "..... gastrointestinal diseases which require a reduction in acid secretion: - duodenal ulcer - gastric ulcer - moderate and severe reflux oesophagitis". The company considered that the term "acid-related disorders" accurately reflected the licence. To make sure that there was no misunderstanding the claim was asterisked and referred to the exact indications of reflux oesophagitis, duodenal ulcer and benign gastric ulcer.

Knoll said that there was no attempt to mislead the prescribing doctor. In fact it was doing the reverse in trying to make it absolutely clear as to the indications.

PANEL RULING

The Panel noted that the summary of product characteristics (SPC) for Protium gave the indication as "For symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion: - duodenal ulcer - gastric ulcer - moderate and severe reflux oesophagitis." The Panel considered that the wording of the SPC was such as to qualify which acid related disorders were licensed indications. The Panel did not consider that Protium was licensed to treat all acid related disorders.

The Panel noted that the claim "Precise control in acid-related disorders" was asterisked to the footnote "Reflux oesophagitis, duodenal ulcer and benign gastric ulcer". The footnote, however, was in small type and would easily be missed by the casual reader. The Panel considered that the immediate impression given by the advertisement was that Protium was licensed for use in all acid related disorders which was not so. The Panel ruled that the advertisement was misleading in breach of Clause 7.2 of the Code.

2 Comparison of interactions on data sheets / SPCs

The product summary booklet (ETH 2240/8/969) was a 24 page A5 booklet which had a number of sections dealing with topics such as chemistry, mode of action, efficacy etc. In a section entitled "Safety and tolerability" there was a table headed "Interactions listed on data sheets/SmPCs". A statement referring to lansoprazole and antacids was "Bioavailability of lansoprazole reduced". This was classified in the table as a known/possible interaction.

COMPLAINT

Wyeth said that this unconditional statement was much broader than the facts as the Zoton (lansoprazole) data sheet stated that antacids might reduce lansoprazole bioavailability if taken within one hour of Zoton ingestion. Wyeth alleged that the section was misleading and disparaging. A breach of Clause 8.1 of the Code was alleged.

RESPONSE

Knoll submitted that the table was a summary and that the interaction between antacids and lansoprazole was categorised under "known/possible interactions". Knoll submitted that this was a perfectly reasonable representation of the facts. The text associated with the table referred to potential interactions. Knoll said that in addition, its representatives had been fully trained on the

use of the table and the fact that it was concomitant use of antacids with lansoprazole that might lead to a reduction in bioavailability. Knoll thought it would be unreasonable that in a summary table it should put all details relating to a possible interaction. The statement was not unconditional and there was no intention to mislead or to be disparaging.

PANEL RULING

The Panel noted that the Zoton data sheet (supplied by Wyeth) stated that "Antacids and sucralfate may reduce the bioavailability of lansoprazole and should, therefore, not be taken within one hour of Zoton".

The Panel considered that the statement in the booklet was not sufficiently clear. It gave a misleading impression as to the duration of the interaction between antacids and Zoton. The statement might lead prescribers to avoid prescribing Zoton and antacids concomitantly whereas this was a feasible option provided that the advice in the data sheet was followed. The statement did not convey the fact that given at least one hour apart there was no interaction between Zoton and antacids. The Panel did not consider the statement disparaged Zoton but, as it did not accurately reflect the position, the statement was misleading. A breach of Clause 7.2 of the Code was ruled.

APPEAL BY KNOLL

Knoll submitted that the use of a summary table highlighting possible interactions associated with products in the same class was perfectly reasonable. Summary tables were frequently used in pharmaceutical advertising material.

Knoll said that its interactions table was just that - a summary, bringing to the prescriber's attention possible interactions that might occur. Only data from the relevant SPCs/data sheets were quoted. The SPC/data sheet for lansoprazole clearly contained a warning that antacids might reduce the bioavailability of lansoprazole. The SPC/data sheet then went on to provide what Knoll would consider to be prescribing information in relation to this possible interaction, in that antacids should not be taken within one hour of lansoprazole. Knoll did not disagree with this. The company did, however, believe it was unreasonable to be expected to provide all details and/or prescribing information for competitor products in a summary table. Knoll submitted that it was inappropriate to provide advice about how to avoid a possible interaction involving a competitor product in a table like the one at issue.

Knoll said that if the table were absolute, then it would not reflect the true situation. It did, however, clearly state "known/possible" interactions in the key, thus removing the need to go into great detail about the nature/features of the potential interaction.

Knoll Ltd believed that this was a balanced summary table, in line with the relevant product SPCs/data sheets. There was no attempt to mislead the prescriber.

APPEAL BOARD RULING

The Appeal Board noted that in addition to an interaction with antacids, the table listed some interactions between lansoprazole and other medicines as 'possible'. The statement regarding the interaction with antacids, however, was not preceded by the word 'possible'. The Appeal Board considered that this gave the impression that the interaction with antacids was absolute compared with the other interactions which were only possible. The Appeal Board noted that, with attention to the timing of administration, the interaction between lansoprazole and antacids could be avoided altogether. The Appeal Board considered that the wording of the lansoprazole/antacid entry in the table did not accurately reflect the situation and was misleading. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 of the Code

The appeal therefore failed.

Complaint received **12 May 1997**

Case completed **8 August 1997**

CASE/AUTH/548/5/97

CONSULTANT PHYSICIAN V MERCK SHARP & DOHME

Promotion of Cozaar

A consultant physician complained about a Cozaar mailing sent by Merck Sharp and Dohme. The mailing included a reprint of a trial published in 1985 which used doses of bendrofluazide four times that which would now be considered appropriate. The complainant considered that it was improper to compare Cozaar with the drugs used in the trial in relation to side effects. The Panel considered that it was unfair to use the trial to highlight tolerability issues when the trial had used what were now regarded as excessive doses of bendrofluazide, a medicine with dose related side effects.

The Panel considered that the use of the phrase "Despite changes in prescribing practice...." was inadequate to put the study into perspective with regard to present day management of hypertension and the tolerability of new therapies. The mailing was unfair and did not reflect the current situation. A breach of the Code was ruled.

A consultant physician complained about a Cozaar mailing he had received from Merck Sharp & Dohme Limited. The mailing consisted of a "Dear Doctor" letter headed "Tolerability with antihypertensive therapies", a reprint entitled "MRC trial of treatment of mild hypertension: principal results", published in the British Medical Journal (BMJ), July 1985, and a postcard. The black and white postcard depicted a crowd scene with a number of the people covered up by a large black cross. The postcard carried the statement "of 17,000 patients in an MRC trial, up to 25% discontinued due to suspected adverse reactions to their medication". This was referenced to the reprint which had been provided.

COMPLAINT

The complainant said that the MRC study provided was designed 20 years ago and used a dose of bendrofluazide four times that considered appropriate now and a considerable dose of propranolol, a beta blocker which was again not very much in use. The complainant considered it improper of Merck Sharp & Dohme to compare Cozaar with the drugs used in this trial in relation to side-effects, and that to promote its product the company had been highly selective in choosing publications with which to make a comparison. The complainant said that Merck Sharp & Dohme had not pointed out that thiazides and beta blockers were of proven value in the treatment of hypertension which was more than could be said for Cozaar.

RESPONSE

Merck Sharp & Dohme said that the mailing had been sent in February, 1997. The reprint of the 1985 BMJ paper was chosen because it was widely recognised as being a landmark study, being one of the first to consider the treatment of hypertension in general practice in the UK. The patient population was over 17,000, and the company was unaware of any more recent UK study of similar magnitude which had superseded this.

Merck Sharp & Dohme accepted that the dosages of bendrofluazide and propranolol used in the BMJ article did not reflect current practice, but this was stated clearly in its covering letter. The company did not consider that this was in any way misleading as it had set this in a balanced, historical perspective, when it stated at the beginning of the second paragraph of the letter "Despite changes in prescribing practice.....".

Merck Sharp & Dohme refuted any suggestion that it had made a comparison between Cozaar and either of the other two products mentioned in the study whether directly or by implication. The purpose of the mailing was to highlight the fact that there had been a high incidence of side-effects associated with commonly used antihypertensive therapy, and this was still a sizeable problem today. There had been no comparison with regard to side-effects and nor had the company attempted to suggest that Cozaar had any mortality data. Indeed, there was no overt mention of Cozaar at all. The mailing was intended to increase awareness of a general issue, namely the incidence of side-effects.

Merck Sharp & Dohme very much regretted that the complainant had interpreted the mailing in the way that he had but nonetheless the company did not believe that it had breached the Code.

PANEL RULING

The Panel noted that the "Dear Doctor" letter itself did not mention Cozaar by either brand name or generic name. Prescribing information for Cozaar was printed on the back of the letter. The Panel considered that the mailing was subject to the Code. It made critical comment about competitors to Cozaar. The letter was headed "Tolerability with antihypertensive therapies" and ended by offering "... a potential solution to such problems ...." by way of a freephone number. The mailing was part of the general promotion of Cozaar.

The Panel noted that the MRC study referred to began in 1977. Patients with mild hypertension, who were randomised to one of two treatment groups, received either bendrofluazide 10mg daily or up to 240mg propranolol daily. These doses were chosen as they were in common use at the time. The Panel noted that the British National Formulary Number 33 (March 1997) stated that in the management of hypertension a low dose of thiazide eg bendrofluazide 2.5mg daily, produced a maximal or near maximal blood pressure lowering effect with very little biochemical disturbance. Higher doses caused more marked changes in plasma potassium, uric acid, glucose and lipids with no advantage in blood pressure control and should not be used. The dose of Aprinox (bendrofluazide) in hypertension was 2.5 - 5mg once daily (ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1996-97). The Panel noted that the dose of propranolol used in the study, ie up to 240mg daily, was still current. The Inderal (propanolol)

data sheet, also in the Compendium, stated that in hypertension the usual dose range was 160-320mg per day.

The Panel noted that the letter gave the doses of bendrofluazide and propanolol used in the study. It then stated "Despite changes in prescribing practice ...." and referred to the need for therapy with fewer side effects as a means for improving patient compliance. The letter did not give the currently recommended dose of bendrofluazide.

The Panel considered that it was unfair to use the MRC study to highlight issues of tolerability when the trial had used what were now regarded as excessive doses of bendrofluazide, a medicine with dose related side effects. The Panel noted that while bendrofluazide and propranolol could still be used to manage hypertension, newer medicines had become available. The Panel did not consider that the phrase "Despite changes in prescribing practice....." was adequate to put the MRC study into perspective with regard to present day management of hypertension and the tolerability of new therapies.

The Panel considered that the mailing was unfair and did not reflect the current situation. A breach of Clause 7.2 of the Code was therefore ruled.

Complaint received **15 May 1997**

Case completed **2 July 1997**

CASE AUTH/550/5/97

CONSULTANT IN PUBLIC HEALTH v MERCK SHARP & DOHME

Provision of mobile bone densitometry service

A consultant in public health complained about an arrangement between Merck Sharp & Dohme and an NHS Trust to purchase the use of a mobile bone densitometry service. It was alleged that the provision of the facility was linked with efforts by the company to promote its product Fosamax. It was further alleged that in so doing Merck Sharp & Dohme had not referred to the Health Authority to check whether the initiative was in line with local healthcare commissioning guidelines, the service had led to the distribution of inappropriate referral guidelines, and it seemed likely to lead to an expectation of future bone densitometry scans, to check responses to treatment, for which no provision had been made.

The Panel noted that the Code permitted the provision of medical and educational goods and services which would enhance patient care and benefit the National Health Service. The provision of such goods and services had to be done in such a way as not to be an inducement to prescribe, supply, administer or buy any medicine. This would often be in disease areas in which the sponsoring company had a commercial interest but it would be unacceptable for such activities to be linked to the prescribing of a particular product.

The Panel noted that the criteria listed in the briefing document included increasing local sales of Fosamax and the number of patients treated with Fosamax was one of the outcomes to be measured. The service was only to be offered to lead specialists who agreed that Fosamax should be used for the active management of patients. The Panel considered that the service was too closely linked to the promotion of Fosamax and ruled it in breach. As far as the referral criteria were concerned, the Panel considered that it was for the lead specialist to ensure that local requirements were met. The Panel did not consider that the industry had been brought into disrepute and ruled no breach of Clause 2 of the Code.

On appeal by both the complainant and Merck Sharp & Dohme, it was the Appeal Board's view that the briefing document associated the bone densitometry service with increased sales of Fosamax. The link between the two was clear. While there were other placement criteria to be satisfied, the service was only provided to those specialists who agreed that Fosamax should be used for the active management of patients. The Appeal Board upheld the Panel's ruling that there had been a breach of the Code.

The Appeal Board acknowledged the complainant's views regarding Merck Sharp & Dohme's lack of consultation with the Health Authority but noted that the company had been in negotiation with a senior clinician. This should have been sufficient. Overall the Appeal Board did not consider that the arrangements for the implementation of the mobile bone densitometry service were such as to bring the industry into disrepute and so upheld the Panel's ruling of no breach of Clause 2.

COMPLAINT

A consultant in public health at a health authority complained about an arrangement between Merck Sharp & Dohme Limited and an NHS Trust to purchase the services of a mobile bone densitometer.

A sum of £25,000 was to be paid by the company into a rheumatology research fund at the NHS Trust. This would in turn be used to purchase the services of a mobile bone densitometer. The initiative was not a research project and had not been referred to the local research ethics committee. The complainant understood that the densitometer would be stationed on Trust premises for a series of two week sessions in 1997/98 and around 500 scans would be carried out. A letter had been written by the Trust's consultant rheumatologist offering the service to local general practitioners (both fund and non-fund holding) free of charge. Certain referral guidelines were included in the letter.

The complainant said that the source of funding for the initiative was not given in the letter but there had been an evening educational event for general practitioners, (sponsored by Merck Sharp & Dohme) at which the arrangement was disclosed. The company's products in the field of osteoporosis were, of course, promoted at that meeting. The complainant did not believe that NHS personnel were receiving any pecuniary advantage as a result of the initiative.

The complainant's main concern was that Merck Sharp & Dohme appeared to have set out to purchase a health care service which was linked to the marketing of a product. In doing so it had neglected recent work carried out by the Health Authority on the relative priority of bone densitometry services, which had led to the establishment of eligibility criteria and a service contract with an NHS provider outside the district. The complainant was also concerned that the Health Authority had not been consulted by the company about its initiative.

The complainant said that unfortunately the guidelines, which were circulated with the invitation to refer, differed in significant ways from the Health Authority's own guidelines and those of the National Advisory Group on Osteoporosis. Another, less important, concern was the probable need for further scans to check the response of any patients put on treatment for osteoporosis following bone densitometry. Ideally this should be done using the same scanner but the complainant was not aware of any plan to provide follow-up in this way.

The complainant summarised his concerns as follows:

- Merck Sharp & Dohme had provided a very large sum of money for the purchase of a health care facility which was intended to identify patients with osteoporosis. This appeared to be linked with efforts by the company to promote its treatment product

- in doing so it had not referred to the Health Authority to check whether the initiative was in line with the local

health care commissioning priorities

- the initiative had led to the distribution of inappropriate referral guidelines

- the initiative seemed likely to lead to an expectation of future bone densitometry scans (to check responses to treatment), for which no provision had been made

The complainant alleged breaches of Clauses 2, 10 and 18 of the Code.

RESPONSE

Merck Sharp & Dohme said that it assumed that the exact complaints were that, by sponsoring a mobile bone densitometry machine ("mobile DEXA"), it had undertaken disguised promotion (contrary to Clause 10.1 of the Code) and, further, that it was an inducement to prescribe its product Fosamax (contrary to Clause 18.1 of the Code). The provision of guidelines which either had not been referred to the relevant health authority or which were "inappropriate" did not appear to be specifically dealt with by the Code, so the company assumed that the complaint in relation to this would fall under Clause 2 of the Code. Merck Sharp & Dohme refuted all the allegations.

In September 1996, Merck Sharp & Dohme made a sum of money available for the provision of mobile bone densitometry services to the NHS. The basis upon which these sums would be allocated was set out in the "Mobile Bone Densitometry Briefing Document", a copy of which was provided. The document gave some background to the current, inadequate, level of provision of the service in the NHS and set out the basis upon which five schemes would be selected and supported by Merck Sharp & Dohme in the UK. The criteria upon which the schemes would be assessed were set out in the document. These included the necessity for a supportive local specialist, guidelines on the way in which the disease could best be managed in primary and secondary care, and the possibility of a reasonable return to the company. Merck Sharp & Dohme accepted the complainant's implied contention that, in supporting these initiatives, it was expecting to see a return on its investment. The company categorically denied, however, that it was in any way directly linked with the marketing of any of its products. Merck Sharp & Dohme recognised that the complainant considered that any initiative sponsored by a pharmaceutical company which was aimed at patient identification in a particular disease area, must, *per se*, be promotion of a product which the company marketed in that disease area. Merck Sharp & Dohme fundamentally disagreed with this contention and considered that it was entirely appropriate for a pharmaceutical company to provide patient identification schemes or facilities on the strict understanding that it was not a *quid pro quo* for prescribing that company's products. Merck Sharp & Dohme contended that this was all it had done in this case.

To deal with this particular scheme, one of Merck Sharp & Dohme's representatives had earlier last year been contacted by a third party (an independent research company with an interest in osteoporosis) regarding an interest shown by the Trust's consultant rheumatologist in establishing the cost of using its mobile bone densitometry machine. Subsequent to the document referred to above, the representative met the rheumatologist in December last year to discuss the possibility of Merck Sharp & Dohme assisting in this regard. The rheumatologist indicated his interest in the scheme and it was agreed that the representative would submit a formal proposal to support the provision of mobile bone densitometry facilities at the Trust. This submission was made in December 1996, supported by a letter from the rheumatologist. It was proposed that Merck Sharp & Dohme should provide a mobile bone densitometry machine to the Trust in early 1997. In fact, the machine was to be made available for three, two week periods. The first two week period commenced in April 1997 and the remaining two periods had not yet occurred.

The availability of this service was notified to local general practitioners by the rheumatologist in a letter with various attachments, one of which was the set of referral guidelines referred to by the complainant. Merck Sharp & Dohme said that it had had no involvement whatsoever with the writing or distribution of the letter or its enclosures. Indeed, the referral guidelines were compiled by the rheumatologist in conjunction with another pharmaceutical company. The company knew that such a letter would be sent and was aware of the contents of the guidelines but it played no part in their dissemination to GPs. This was quite deliberate; whilst Merck Sharp & Dohme had no intention of understating its involvement with the project, it believed that any mention of its supporting the initiative in the invitation letter might well convey an inappropriate and misleading impression. In addition, the availability of the service was "launched" at a meeting held in March 1997 at the Trust's postgraduate centre. The meeting confined itself to the availability and mechanics of the service and was PGEA approved. Merck Sharp & Dohme had previously been asked to sponsor the meeting and had agreed to do so. As was normal in these circumstances, its sponsorship involved defraying the cost of reasonable hospitality at the meeting and erecting a small promotional stand outside the room in which the meeting was to take place. While this was the sum total of Merck Sharp & Dohme's involvement, it was made clear at the meeting that the service was being supported by a financial grant from the company. In response to a question from the floor, the rheumatologist also made it clear that the company's financial commitment was limited to a total of six weeks' provision of the service. Among those attending the meeting was another consultant in public health at the same health authority as the complainant. Neither at that meeting nor at any subsequent time had he indicated to Merck Sharp & Dohme that the Health Authority was in any way uneasy about either the provision of the service or the company's involvement with it. In these circumstances, the complaint had come as something of a surprise.

Merck Sharp & Dohme noted that the rheumatologist had met the complainant in March this year, prior to the first two week session with the mobile bone densitometry machine, and discussed the proposal in detail with him. The company believed that the complainant had recently written to the rheumatologist indicating his disquiet with its involvement and mentioning to him the substance of his complaint.

Merck Sharp & Dohme responded as follows to the

specific concerns of the complainant:

1 The company accepted that a sum of money had been given to an NHS Trust for the purchase of bone densitometry scans intended to identify patients with osteoporosis. This money had been provided by way of gift and the company denied categorically that it was in any way linked with its efforts to promote Fosamax. The company hoped and expected that the service would identify a number of patients with established osteoporosis in need of relevant treatment. The actual form of this treatment, however, was entirely at the discretion of the relevant clinician. Given that the full amount of £25,000 had already been given to the Trust, provision of this funding could not in any way be dependent on the clinicians prescribing Fosamax. They were entirely free to prescribe whatever product they thought was in the best interests of the patients identified by this service.

2 Merck Sharp & Dohme accepted that it did not specifically gain endorsement from the relevant health authority prior to initiating the service. The company pointed out, however, that it was in full consultation with the relevant NHS Trust. It was also aware that the clinician providing the service at the Trust was in consultation with the Health Authority and, further, one of the complainant's colleagues attended the launch meeting for the service and did not in any way indicate any concern whatsoever with either the scheme or Merck Sharp & Dohme's involvement with it.

3 Merck Sharp & Dohme disagreed that the referral guidelines were inappropriate. While the company did not write the guidelines itself, it had reviewed them thoroughly and believed them to be both clinically responsible and consistent with the National Advisory Group on Osteoporosis report referred to in the complaint. Merck Sharp & Dohme contended that it had never seen the Health Authority guidelines referred to by the complainant and so was not in a position to comment on their consistency with those issued by the rheumatologist. Merck Sharp & Dohme noted that when one of its representatives met the complainant in April 1997, to discuss other matters, she was told that these guidelines were still in a consultation phase and had been sent out for comment. The complainant promised to send a copy of the final document when it was available, although to date this had not been received.

4 Merck Sharp & Dohme accepted that its involvement with the scheme was limited to provision of a machine for a total of six weeks. It was the rheumatologist's hope that this would be sufficient to demonstrate to the Health Authority that such a scheme would be sufficiently welcomed by local GPs that its funding should be a priority for the Health Authority. Whether or not this proved to be the case was, of course, a matter entirely for the Health Authority. Merck Sharp & Dohme refuted any suggestion that the provision of the service for a limited time, in order to enable informed judgements to be made about the need for it, was in any way inappropriate or a breach of the Code.

Accordingly, therefore, Merck Sharp & Dohme considered that its involvement in the scheme was non-promotional and fell squarely within the supplementary information to Clause 18.1 of the Code. The company also contended that it had not breached any provision of the Code, particularly in this case Clauses 10.1 or 2.

PANEL RULING

The Panel noted the supplementary information to Clause 18.1 stating that "Clause 18.1 does not prevent the provision of medical and educational goods and services which will enhance patient care or benefit the National Health Service. The provision of such goods or services must not be done in such a way as to be an inducement to prescribe, supply, administer or buy any medicine". The Panel recognised that such goods and services would often be in disease areas in which the sponsoring company had a commercial interest. Such activities might facilitate the market development of the sponsoring company's products but this was not necessarily in breach of the Code. It would be unacceptable for such activities to be linked to the prescribing of a particular product. The Panel considered that the provision of money to pay for mobile bone densitometry services would enhance patient care and benefit the NHS but the important question was whether or not the funding met the requirements of Clause 18.1.

The Panel noted that five schemes were to be chosen with the marketing department providing a budget of £10,200 for each of the five projects to cover rental of the machine including delivery, warranty, maintenance and training. The "Mobile Bone Densitometry Briefing Document" provided by Merck Sharp & Dohme set out the criteria upon which these would be selected. One of the criteria to be satisfied was that there had to be a supportive local lead specialist who agreed that ".... Fosamax should be used for the active management of patients". The Panel noted that the placement criteria were as follows:

"1 High potential area (in terms of demographics and sales).

2 Supportive local lead Specialist who agrees that:

- DEXA is the gold standard and should be used in targeted patients;
- GPs have a major responsibility in the shared care of osteoporotic patients;
- MSD can help select the GPs to participate,
- FOSAMAX should be used for the active management of patients.

3 Guidelines. Shared care guidelines should be developed, allowing and encouraging GPs to interpret the results and manage patients accordingly.

4 Supportive GPs. A group of GPs should be identified who were interested in osteoporosis, will actively use guidelines and manage their patients accordingly and would value the service to the point where they would campaign for the Health Authority to support its availability.

5 Audit. The placement sites should be willing for us to participate in an audit of the project - it is as important for them to justify the process as it is for us. They will need support from the Health Authority to continue the project when we move elsewhere."

The Panel noted that the briefing document listed patient

criteria and stated that based on the criteria 200 scans would be needed each year for 100,000 population. Five objectives were listed these being:

"Facilitate the earlier diagnosis and active management of osteoporosis in the Primary Care environment.

Efficiently utilise mobile DEXA equipment loaned by MSD for a period of 1 year to provide diagnostic technology to areas with a great need.

Facilitate the process of development and implementation of shared care guidelines placing greater responsibility with the General Practitioner for the diagnosis and management of the disease.

Use utilisation and diagnosis data to convince local Purchasers and Providers that a targeted scanning policy is affordable and warranted.

Increase local sales of FOSAMAX through the above."

The document stated in a section headed "Strategy" that "Through well researched and rational placement of mobile DEXA technology in the community, co-ordinated through the Primary and Secondary Care sectors, we will significantly increase the number of patients diagnosed as osteoporotic. When combined with shared care guidelines promoting active GP management and Fosamax, increased rational usage of our product will be ensured". The document also stated that the measurement of three main outcomes was an absolute requirement, these being; the total numbers of patients using the scheme and their reason for referral, the number of positive diagnoses of osteoporosis made using the scheme and the number of patients treated with Fosamax.

The Panel was concerned that the briefing document linked the service to increased use of Fosamax. The document stated that the "co-ordination of the project will require considerable attention, therefore, time commitment on the part of the local representative". The Panel did not have any documents relating to instructions for representatives.

The Panel considered that in order for a service to meet the requirements of the supplementary information to Clause 18.1 of the Code it should not be directly linked to increasing prescribing of a specific product. The Panel noted that the scheme was only to be offered via lead specialists who agreed that Fosamax should be used for the active management of patients. It was run by the company's marketing department with the involvement of representatives. The Panel acknowledged that it was for the doctor to decide which treatment if any to give to patients but, by only offering the service via specialists who agreed that Fosamax should be used, Merck Sharp & Dohme was increasing the likelihood that a prescription for Fosamax would be written. The Panel considered that the bone densitometry service was too closely linked to the promotion of Fosamax. This in effect meant that the service was unacceptable. The Panel ruled a breach of Clause 18.1 of the Code.

The Panel considered that goods and services offered under Clause 18.1 of the Code had to be non-promotional. They must not bear the name of any medicine but might bear a corporate name. The Panel considered that it would have been preferable if the role of Merck Sharp & Dohme had been explained in the letter from the consultant rheumatologist offering the bone densitometry service to local GPs. The role of Merck Sharp & Dohme had been explained to the GPs attending the meeting. The letter to the GPs referred to the availability of the machine and provided a referral form. There was no mention of any products. The letter mentioned that following the scan the consultant would forward the results of the suggested guidelines for interpretation and management. In the Panel's view the letter was not disguised promotion and the Panel therefore ruled no breach of Clause 10.1 of the Code. The requirement in the Code relating to declaration of sponsorship (Clause 9.9) only referred to material relating to medicines sponsored by a pharmaceutical company and did not therefore apply.

The Panel noted that Merck Sharp & Dohme had not written the guidelines itself, but had reviewed them and believed that they were both clinically acceptable and consistent with the National Advisory Group on Osteoporosis report. The Panel further noted that the complainant had told one of its representatives in April that the Health Authority's guidelines were still in consultation phase and had been sent for comment.

The Panel noted that the complainant, in response to a request for further information, had provided a copy of a paper from a Health Authority working group which detailed referral protocols in the area of bone densitometry for osteoporosis. The local protocol was put forward and accepted, in principle, by the Health Authority in October 1996 with the proviso that comments from other named organisations would be considered at the next meeting. Clinical indications for bone densitometry were: oestrogen deficiency; vertebral deformity and/or multiple low trauma fractures; long term corticosteroid use; causes of secondary osteoporosis and monitoring therapy (to check response to treatment). The guidelines for referral as set out in the letter from the consultant rheumatologist differed slightly and were: peri-menopausal women in whom the decision to take HRT would be influenced by the knowledge of bone density; premature menopause or prolonged amenorrhoea; previous low trauma vertebral, hip, wrist or ankle fracture; osteoporosis reported on spinal x-rays; long term treatment with steroids; disorders known to cause osteoporosis and a strong family history of hip or other fractures. The Panel noted that five schemes were to be funded and considered that referral criteria would almost certainly vary around the country. The Panel considered that having been provided with funds by Merck Sharp & Dohme to run a bone densitometry service it was for the lead specialist to ensure that the referral criteria were within the local guidelines.

The Panel did not accept that the arrangements were such as to be in breach of Clause 2 of the Code. The Panel therefore ruled no breach of Clause 2 of the Code.

APPEAL BY MERCK SHARP & DOHME

Merck Sharp & Dohme appealed against the ruling of a breach of Clause 18.1.

Merck Sharp & Dohme said that the central document to this finding seemed to be the document entitled "Mobile Bone Densitometry Briefing Document". In ruling a breach, the Panel seemed to have taken particular note of certain statements contained in that document:

"...Supportive local lead Specialist who agrees that ... FOSAMAX should be used for the active management of patients" (in the section headed "Placement Criteria").

"...Increase the local sales of FOSAMAX through the above" (in the section headed "Objectives").

"...When combined with shared care guidelines promoting active GP management and FOSAMAX, increased rational usage of our product will be ensured." (In the section headed "Strategy").

"...The coordination of the project will require considerable attention, therefore, time commitment on the part of the local representative" (in the section headed "Planning and Coordination").

1 Introduction The project, as with any such project undertaken by Merck Sharp & Dohme, was intended to assist the NHS in optimising its resources by the rational use of pharmaceutical products. Merck Sharp & Dohme believed this to be an entirely reasonable aim, and one which was consistent with the requirements of evidence-based medicine. One of the most pressing problems in the effective management of osteoporosis in the UK was identification and diagnosis of patients at risk of the disease. A diagnosis of osteoporosis often followed a secondary event, such as a low-trauma fracture, when the disease might well be in an advanced stage of its pathology. Merck Sharp & Dohme believed that NHS resources in this area might be optimised by the effective diagnosis of patients with established osteoporosis from the pool of those patients most at risk and the rational prescribing of the appropriate products for those patients. Forearm DEXA facilities were one way of arriving at this diagnosis.

Merck Sharp & Dohme was also aware that health authorities were cash-limited and therefore needed to prioritise the services which they offered to patients living in their areas. This frequently led to the paradox that a health authority could not decide whether a particular service should be a priority without first funding it on a trial basis; however, such funding was not available because the service was not yet deemed to be a priority. The Merck Sharp & Dohme mobile bone densitometry service was aimed at breaking this paradox by allowing a number of NHS providers to offer this service, on a trial basis, in order that they could evaluate its effect and thus present a detailed case for prioritisation of the service to their health authority.

Merck Sharp & Dohme was quite clear, however, that this project also had a commercial objective. Merck Sharp & Dohme believed Fosamax to be the most effective treatment for established osteoporosis in post-menopausal women. This view was supported by a wealth of clinical evidence, most notably the Fracture Intervention Trial. Merck Sharp & Dohme's representatives promoted Fosamax on this basis. Accordingly, Merck Sharp & Dohme would expect that a proportion of the osteoporotic patients diagnosed by this service would be prescribed Fosamax.

Nevertheless, and Merck Sharp & Dohme believed this to be a crucial distinction, there was no compulsion on the physician taking part in the project to prescribe Fosamax in return for receiving funding from Merck Sharp & Dohme. Indeed, the entire cost of each of the five schemes in the project was met by Merck Sharp & Dohme at the outset and thus there was no way that it could withdraw a scheme should it not lead to a demonstrable increase in Fosamax sales. Merck Sharp & Dohme would certainly agree that any such project which was dependent upon patients being prescribed a particular product would certainly be objectionable and a breach of the Code. Merck Sharp & Dohme emphasised, however, that that was not the case here.

2 Placement Criteria "...To achieve our objectives the following criteria for placement should be satisfied.... Supportive local led Specialist who agrees that .... FOSAMAX should be used for the active management of patients."

Clearly, as only five schemes were being funded, there must be a number of criteria upon which those five would be selected. Merck Sharp & Dohme believed it was both commercially prudent and entirely ethical that one of those criteria should be that the physician implementing the scheme should not be particularly adversely disposed to using Merck Sharp & Dohme's products. Merck Sharp & Dohme would point out, however, that this criterion was only one among a number of others, which were aimed at ensuring that each scheme would have the maximum impact, in terms of patient care and clinical return, for the investment being made. This investment was not restricted to Merck Sharp & Dohme funding but also included the considerable time and effort required of the implementing physician in planning, implementing and analysing each scheme. As could be seen from the briefing document, it was particularly important that each scheme should lead to effective implementation of rational shared care guidelines in the area concerned. Merck Sharp & Dohme had no control over the content of these guidelines and they might easily, therefore, advocate the use of competitor products instead of, or in addition to, Fosamax.

Accordingly, while Merck Sharp & Dohme accepted that one of the criteria was that the implementing physician should support the use of Merck Sharp & Dohme's product, this was only one of a number of criteria aimed at ensuring that patients received the maximum benefit possible from the project.

3 Objectives "...Increase the local sales of FOSAMAX through the above."

In this statement "the above" referred to were the other four objectives of the project. These were: early diagnosis and active management of osteoporosis, efficient use of the DEXA equipment, facilitating the development and implementation of shared care guidelines and use of the data to convince local decision-makers that a forearm DEXA service should be a priority in their area. Given Merck Sharp & Dohme's view, outlined above, that Fosamax was the rational choice for the treatment of osteoporosis in post-menopausal women, Merck Sharp & Dohme believed that fulfilment of the first four objectives would lead to increased sales of Fosamax in that area. This was simply Merck Sharp & Dohme's hope and expectation, however, and was in no way a condition of implementing the project in any given area.

4 Strategy "....When combined with shared care guidelines promoting active GP involvement and FOSAMAX, rational usage of our product will be ensured."

Merck Sharp & Dohme supported and endorsed the rational use of its products, and for the reasons set out above it maintained that shared care guidelines reflecting the principles of evidence-based medicine would increase the rational use of Fosamax, and thus its sales. This was in no way directly linked to participation in this project.

5 Measurement "...From our perspective, the measurement of three main outcomes will be an absolute requirement in addition to any others ... number of osteoporotic patients treated with FOSAMAX."

This section dealt purely with measurement of the success of the project. Merck Sharp & Dohme accepted that one of the criteria upon which the success of the project would be measured was an increase in the number of patients for whom Fosamax was prescribed. This was based on Merck Sharp & Dohme's views regarding the place of Fosamax in the rational treatment of osteoporosis. It did not in any way indicate that such an increase in sales was a prerequisite to placement of the project in a particular area.

6 Planning and Coordination "....The coordination of the Project will require considerable attention, therefore, time commitment on the part of the local representative."

This comment was linked to the further criticism by the Panel that "[the project] was run by the company's marketing department with the involvement of representatives...". The project was organised and administered by Merck Sharp & Dohme's marketing department as "product champions" for Fosamax. Whether such a project should, in fact, be run by a company's medical department, or some other department, was an issue upon which Merck Sharp & Dohme would welcome the Appeal Board's comment. So far as day to day implementation was concerned, this was the responsibility of the local representative purely on the basis that they alone had the requisite detailed local knowledge and day to day contacts which would enable the project to be a success. Merck Sharp & Dohme simply did not think it was feasible for the detailed running of the project to be handled by a centralised, headquarters-based department. In any event, Merck Sharp & Dohme did not believe that the simple fact that the project was run by marketing and sales departments of the company should be enough to render it a breach of the Code.

In planning, approving and implementing this project, Merck Sharp & Dohme believed that it was adhering to the highest standards of clinical ethics. Merck Sharp & Dohme was, therefore, concerned that, nonetheless, the Panel ruled that it was in breach of the Code. Merck Sharp & Dohme had also noticed a significant increase in the number of like projects being undertaken by pharmaceutical companies, where these companies defrayed the cost of diagnostic procedures where their costs had traditionally been met by the NHS. These projects varied widely in terms of their scope, content and implementation. Merck Sharp & Dohme, therefore, believed it was vital to the best interests of the industry for the Appeal Board to give detailed guidance to companies regarding the acceptability of such projects and how they might appropriately be implemented.

APPEAL BY THE COMPLAINANT

The complainant appealed against the ruling of no breach of Clause 2.

The complainant said that naturally he was pleased that his complaint had been upheld with regard to Clause 18.1 of the Code of Practice. The material submitted by Merck Sharp & Dohme (the "Mobile Bone Densitometry Briefing Document") was, of course, not previously known to him. The complainant was shocked by the close linkage it revealed between the funding of bone densitometry by the company and the promotion of a particular product, Fosamax. This linkage was shown, firstly, by the targeting of this generous scheme only towards consultants who accepted that Fosamax should be used for the active management of patients; secondly, by the clearly stated objective within the strategy to increase the sales of Fosamax; and thirdly, by the company's decision to audit the scheme by measuring the number of patients scanned who were then started on Fosamax. The complainant was also concerned about the stated intention of the scheme to recruit sympathetic general practitioners to campaign for the increased provision of bone densitometry by the Health Authority.

It was evident that the local arrangement was not a "one-off", with a total of five schemes being planned each with substantial funding. The complainant was not sure how many of the schemes had actually taken place though he was aware of one other. The extracts from Merck Sharp & Dohme's own document suggested to him that the company had made a systematic attempt to both market its products and influence health care commissioning through the purchasing of bone densitometry services.

The actions of a pharmaceutical company in relation to Clause 2, were more difficult to assess as no objective criteria were laid down. It seemed to the complainant that this was the section which dealt with the relationship between the pharmaceutical industry and other organisations, such as health authorities and NHS trusts. Indeed there was no other part of the Code that specifically covered these relationships. Speaking from his own perspective, as an employee of a health authority, he still had serious reservations about the behaviour of Merck Sharp & Dohme in this instance. Therefore, he wished to appeal against the Panel's ruling that there was no breach of Clause 2 of the Code.

The complainant commented on the statements made by Merck Sharp & Dohme in response to his complaint which he said were potentially misleading in several respects.

1 The company argued that the payment of £25,000 was made before the scheme began and, therefore, could not influence subsequent prescribing. This was undermined by its own admission that only lead specialists who agreed that "Fosamax should be used for the active management of patients" would be included. The intention was, therefore, to pre-select clinicians who would be more likely to recommend Fosamax. It was very clear that the rheumatologist's effect on local prescribing patterns had been carefully assessed by Merck Sharp & Dohme. The company was confident that extending the numbers of new patients diagnosed as osteoporotic would translate directly into extra sales of Fosamax.

2 The first information that the Health Authority received about this scheme was when a colleague accidentally saw a letter from the consultant rheumatologist to local general practitioners, inviting them to refer patients. This was at the beginning of March 1997. It was clear that the scheme had already been fully planned at that stage and indeed the funding had been agreed as early as December 1996. Therefore, the statement in Merck Sharp & Dohme's response that "the clinician providing the service at the Trust was in consultation with the Health Authority" was misleading, if it was intended to imply that the Health Authority had been informed about the proposed scheme. No indication of the proposed scheme had been given to the Health Authority by the rheumatologist, the Trust or the company.

It was true to say that the Health Authority was aware of the rheumatologist's interest in establishing a local bone densitometry service and a business case for such a service had been received and turned down. The chief executive of the Trust had written to the Health Authority in October 1996 confirming that the Trust had put this proposal "on ice".

On learning of the referral invitation, the complainant immediately contacted the rheumatologist to find out more and express concern that the Health Authority had not been consulted. The chief executive of the Health Authority telephoned his opposite number at the Trust with the same concerns and followed these up with a letter in March 1997. The chief executive of the Trust was also unaware of the scheme, which suggested that Merck Sharp & Dohme's efforts to consult within the Trust had not been thorough. The complainant met the rheumatologist, with a colleague from the Health Authority, in March to repeat their concerns. It was evident that the scheme could not be stopped at that stage, as well over 100 local general practitioners had been invited to refer and had already begun to respond.

The complainant hoped that this demonstrated that the Health Authority had made plain its concerns about the scheme, both formally and informally, to the Trust, as soon as it became aware of what was happening. The suggestion that the Health Authority had tacitly approved the scheme, because a consultant in public health medicine attended the "launch meeting", was quite incorrect. This was an educational meeting for general practitioners and other doctors taking place after the scheme had been finalised between the pharmaceutical company and the Trust. It could not be considered an appropriate opportunity for the Health Authority to respond to the scheme. The complainant subsequently met a representative of Merck Sharp & Dohme in April 1997 regarding another matter, and clearly described his concerns about the company's bone densitometry scheme.

3 The referral guidelines on bone densitometry which were issued to general practitioners, with the invitation to refer, were neither the same as those agreed by the Health Authority, nor those recommended by the Advisory Group on Osteoporosis. The most significant difference was the addition of a category for patients with a strong family history of hip or other fractures. This would tend to increase the potential application of bone densitometry considerably.

The purpose of making this point was not to quibble about the exact guidelines but to show how prior consultation with the Health Authority could have ensured that a consistent message was given to general practitioners, rather than the very confusing picture that had ensued. The complainant did not think that Merck Sharp & Dohme could pass the responsibility for this situation wholly to the consultant or the Trust, as the company was a prime mover in the arrangement and appeared to have both scrutinised and approved the guidelines.

The comment made by the Merck Sharp & Dohme representative to the effect that the Health Authority guidelines were still in the consultation phase in April 1997 was incorrect. The complainant had previously submitted information to the Code of Practice Authority showing that the guidelines were adopted in principle at a Health Authority meeting in October 1996 and confirmed, after consultation, in November 1996. The comment from Merck Sharp & Dohme actually related to a Health Authority newsletter which had not yet been issued.

4 This response from Merck Sharp & Dohme seemed to play down the importance of the bone densitometry scheme and implied that it was not intended to pressurise the Health Authority into changing its purchasing policy on bone densitometry. The complainant's response to this was four-fold:

i) The purchasing of over 500 scans (at a total cost of £25,000) was a very substantial input when focused on a single disease problem in a small district. Taken together with the Health Authority funded service at another location, this would represent more than one year's need for scans in a district with a fully developed osteoporosis screening and treatment service. It was vastly in excess of the previous demand for bone densitometry in the area, as measured by referrals to NHS densitometry facilities. Thus the effect of the company's actions could reasonably be expected to have an important impact on the Health Authority.

ii) The evidence given by Merck Sharp & Dohme confirmed that the company saw this initiative as a way of influencing the Health Authority's commissioning priorities. Indeed, the injection of new resources into a service, for a limited period, was a classic method of forcing change in a particular direction. It was often termed "pump priming" and worked on the basis that it was very difficult to remove or scale down a service once it had been brought into existence. One of its effects was to place the organisation which was expected to continue the funding (in this case the Health Authority) in the position of either cancelling the service, against public or professional opposition, or having to rethink its investment plans in order to provide continuing finance. In view of these serious implications, the complainant found it extraordinary that Merck Sharp & Dohme did not seek to inform or consult with the Health Authority.

iii) An additional issue in this case was the need for rescanning of patients who had been started on treatment for osteoporosis, after a minimum of two years, to check that the condition was improving. Expert advice suggested that this must be done using the same machine, as otherwise the results were not comparable. By funding the provision of around 500 scans the pharmaceutical

company was inevitably storing up a group of patients who would need rescanning on the same machine in two years' time. As this was a private facility there was no guarantee that the Health Authority would be able to offer this service. The complainant thought that consultation with the Health Authority was needed to address this issue.

iv) The complainant was also concerned that part of the marketing strategy in this scheme was the identification of a group of local GPs to support the provision of bone densitometry by means of a campaign to influence the Health Authority. The Health Authority did lay great importance on the advice of general practitioners when planning services but it was essential that this advice was independent and not influenced by factors other than the perceived needs of patients. In the complainant's opinion the involvement of pharmaceutical companies in orchestrating local medical opinion was not acceptable. If it occurred at all, it should be done openly. In this case it was unfortunately not clear whether Merck Sharp & Dohme intended to acknowledge its involvement in the campaign.

The complainant said that the above comments were designed to uphold his original complaint, as follows:

- that Merck Sharp & Dohme should have informed and consulted with the local Health Authority regarding a scheme that would have substantial implications for health care commissioning and prescribing costs

- the company had both the time and the opportunity to do this, but failed to do so

- the initiative led to the distribution of referral guidelines materially different from those which the Health Authority had agreed

- that a likely result of the scheme would be difficulty in providing optimal care for a sub-group of patients needing further scans.

The above list of faults, in itself, had served to reduce the complainant's confidence and that of colleagues at the Health Authority in the pharmaceutical industry. However, this had been compounded by the perception in this case that the company might have set out to influence Health Authority decision making without openly acknowledging its intention and involvement. The complainant was sure that other members of the pharmaceutical industry would be concerned at the targeting of resources towards an influential clinician who was thought to be favouring one company's products at the expense of another.

RESPONSE FROM MERCK SHARP & DOHME

Merck Sharp & Dohme said that the central complaint made against it seemed to be that it implemented the mobile bone densitometry service without having first discussed it with the Health Authority. The complainant made specific comment on a number of matters appearing in previous correspondence and also noted that this alleged breach had led to two other consequences which he believed flowed from it ("the distribution of referral guidelines" other than those distributed by the Health Authority and "difficulty in providing optimal care for a sub-group of patients needing further scans"). These did not, however, appear to be the actual breach of Clause 2 of the Code which was alleged. Merck Sharp & Dohme proposed to answer the letter of appeal on that basis although, perhaps, the complainant would indicate if that was not the case.

As Merck Sharp & Dohme had previously stated, it did not believe that it had breached Clause 2 (or, indeed, any other clause) of the Code by providing the service. Merck Sharp & Dohme accepted that it did not directly inform the complainant of the service; in fact, it did inform one of his colleagues in early March of this year. In any event, Merck Sharp & Dohme believed this disclosure to be irrelevant. Merck Sharp & Dohme's submission was that it was under no obligation to inform the Health Authority of the service and thus the failure to do so was not a breach of the Code.

It was not clear whether the complainant was suggesting that, in all cases, companies should consult with the relevant health authority before "... purchasing ... healthcare services or facilities ... on behalf of NHS providers or general practitioners ..." or whether they were obliged to do so only where the purchase led to the consequences which the complainant mentioned. Merck Sharp & Dohme did not believe that the former was necessary, nor that the latter was workable as it would involve any Code of Practice investigation into such activities focusing more on the perceived consequences of a service, than on the quality of the service itself.

In cases such as this, where a pharmaceutical company made a grant to a physician to enable him or her to purchase services for their patients, Merck Sharp & Dohme would submit that it was the responsibility of the physician to ensure that necessary permissions had been obtained. Given that, in most cases, the company would not know how a particular health authority, trust, hospital or practice organised itself and its responsibilities internally, it was simply not practical to place responsibility for seeking the relevant approvals on the company in question.

It was worth noting that, in this case, the rheumatologist was rather surprised that when the complainant and one of his colleagues met him in March to discuss the service, the complainant criticised both him and Merck Sharp & Dohme for failure to so notify the Health Authority. The rheumatologist disagreed strongly that either he or Merck Sharp & Dohme was obliged to seek approval from the Health Authority for the service. Indeed, the rheumatologist so informed the complainant at the meeting between them in March.

It was clear, therefore, that Merck Sharp & Dohme disagreed with the central tenet of the complaint. Merck Sharp & Dohme did not believe that, in situations such as these, health authorities had a right to be "informed and consulted" before such a service could proceed. In any event, if the Appeal Board nonetheless ruled that they did have such a right, Merck Sharp & Dohme would submit that it was for the physicians who received the service to do so. They were in the best position to justify the service in the context of local needs, and they would almost always know the relevant decision-making process better than the company which simply provided funds.

Notwithstanding, the complainant alleged certain consequences of Merck Sharp & Dohme's failure to

"inform and consult" with him, and Merck Sharp & Dohme dealt with these in the order in which the complainant presented them:

1 Merck Sharp & Dohme's submission was that, by meeting the whole cost of the service in advance, it could not be seen as an influence on subsequent prescribing. The complainant disagreed, noting that Merck Sharp & Dohme's briefing document stated that the service should be offered to " ... Supportive local lead specialists[s] who agree that ... FOSAMAX should be used in the active management of patients". Merck Sharp & Dohme made two points in reply: firstly, there was only funding for a small number of such services and, therefore, there must be criteria for selection: it would be commercially imprudent for any company to support such a service in any locality where the local opinion leaders were vehement critics of their products. Thus Merck Sharp & Dohme believed it was entirely reasonable to require that local specialists were at least supportive of the use of its products in appropriate patients. This was very far, however, from requiring them to prescribe Merck Sharp & Dohme's products in return for provision of the service, which Merck Sharp & Dohme would certainly see as a breach of the Code.

Secondly, it was also a pre-condition to providing the service that "... shared-care guidelines should be developed, allowing and encouraging GPs to interpret the results and manage patients accordingly". Even if, therefore, the local specialist was a supporter of Fosamax, Merck Sharp & Dohme clearly envisaged that most of the prescribing which arose from the diagnosis of osteoporotic patients would be done by GPs rather than the specialist, and would be done under guidelines which supported rational treatment of the disease. This treatment might or might not involve Fosamax, depending on the circumstances of each patient, but was certainly not something which could be controlled by Merck Sharp & Dohme.

2 Merck Sharp & Dohme was initially introduced to the rheumatologist by the independent research company which had been approached by him and a colleague in late 1996 to investigate the possibility of providing a service such as the one Merck Sharp & Dohme eventually supported. The rheumatologist had a substantial amount of money in a research fund and was trying to decide whether the needs of his patients could best be met by renting a DEXA machine (in a similar manner to the service) or by buying a machine outright. The problem with the latter course of action was that he did not have the money to fund its ongoing running costs and he had put a business case to the NHS Trust in respect of the latter. The research company, which had previously worked with one of Merck Sharp & Dohme's representatives, suggested that the rheumatologist approach Merck Sharp & Dohme. This approach took place in December 1996 and happened to coincide with the release of the briefing document which was before the Appeal Board.

Merck Sharp & Dohme agreed to fund the service in late December 1996 and there were two meetings (in January and February 1997) between two of its representatives and the rheumatologist and a colleague to discuss the logistics of the service. The rheumatologist informed Merck Sharp & Dohme that in early 1997 he had been approached by the Health Authority and asked to sit on an advisory committee on osteoporosis. In addition, he had also told Merck Sharp & Dohme that he had been telephoned by a senior registrar at the Health Authority and asked to comment on their (at that stage) draft referral guidelines. Merck Sharp & Dohme assumed, therefore, that the rheumatologist would make whatever disclosure he deemed fit, if any, regarding the service to his close contacts at the Health Authority. Merck Sharp & Dohme believed it perfectly reasonable to have done so.

Whilst Merck Sharp & Dohme did not feel obliged to inform the Health Authority of the service in advance, Merck Sharp & Dohme did, in fact, do so. In March 1997, one of Merck Sharp & Dohme's representatives met a consultant in public health at the Health Authority. The purpose of the meeting was to discuss any ongoing project with him which Merck Sharp & Dohme was involved with; however, Merck Sharp & Dohme's representative also briefed him about the service at that meeting. He raised no objections to it at that stage, nor had he done so since. Merck Sharp & Dohme therefore found it rather strange that the complainant should have made this complaint. Merck Sharp & Dohme would be grateful to learn whether there was an established guideline on such partnerships between industry and the NHS in place at the Health Authority, which supported this complaint, and, if so, how two employees of the Authority could interpret it in such different ways. Also, in discussing this appeal with the rheumatologist, he informed Merck Sharp & Dohme that not only did the consultant in public health attend the launch meeting of the service in March 1997 but that the complainant also attended the meeting. Even if the meeting was not " ... an appropriate opportunity for the Health Authority to respond to the scheme ..." (with which Merck Sharp & Dohme disagreed) it would surely have been a good moment to at least mention the Health Authority's disquiet with the service. In fact, the first time Merck Sharp & Dohme was made aware of the complainant's views was at a meeting between him and another of Merck Sharp & Dohme's representatives in April 1997, when they met to discuss another issue. The complainant mentioned that he had concerns regarding the service and the representative asked whether there was anything which she could do to allay his concerns. He replied that there was not and, as far as she was concerned, it was left at that.

Merck Sharp & Dohme believed that the complainant was quite right to raise his concerns with the rheumatologist and the Trust early in March and Merck Sharp & Dohme also believed that this was a matter entirely between them. Merck Sharp & Dohme did not raise any particular objection to the fact that the complaint was made some two months after the Health Authority was first made aware of the service, as it did not think the complaint should have been levelled against it at all.

3 Merck Sharp & Dohme accepted that the referral guidelines issued by the rheumatologist differed slightly from those stated in the AGO (Advisory Group on Osteoporosis) report. Merck Sharp & Dohme still had not seen a copy of the Health Authority guidelines so it could not comment on these. Nevertheless, Merck Sharp & Dohme believed all this to be irrelevant to this complaint. The guidelines were written by the rheumatologist and

represented his clinical judgement; Merck Sharp & Dohme did not believe that the complainant was suggesting that they were in any way clinically improper, simply that they differed from those written by the Health Authority. It must surely be open to clinicians to have different, but each perfectly acceptable, clinical opinions. If the complainant believed that the rheumatologist's guidelines should not be promulgated, that was a matter between them.

The rheumatologist did not believe that the differences between the two sets of guidelines would "increase the potential application of bone densitometry considerably"; again, that was a matter for them to discuss. Merck Sharp & Dohme knew the guidelines were to be issued and saw them in advance; however, it played no part whatsoever in their writing or distribution. That was undertaken entirely by the rheumatologist. Had the guidelines been in any way clinically irresponsible, Merck Sharp & Dohme would have progressed the service no further. This did not seem to be the allegation and Merck Sharp & Dohme therefore believed that any further discussion on the appropriateness of the referral guidelines should take place between the rheumatologist and the complainant. Merck Sharp & Dohme certainly did not believe that it had breached the Code in this regard.

4 Merck Sharp & Dohme fundamentally disagreed with the complainant in this regard. As Merck Sharp & Dohme had mentioned in a previous submission in this matter, it had provided this service in an attempt to help break a paradox which physicians frequently encountered. They could not have a particular service established as a priority for trust or health authority funding without showing a real need for the service in their area; however, there was no funding available to help establish that need because the service was not yet deemed a priority. By providing funding for the service, Merck Sharp & Dohme was enabling a number of physicians to demonstrate a real need for the service, to a trust or health authority. This then became another piece of evidence for the trust or health authority to bear in mind when setting overall priorities. It did not force them into doing anything against their better judgement; it simply enabled evidence to be properly gathered for their deliberation. This was particularly true in cases such as the present, where it was made quite clear to general practitioners at the very outset (at the launch meeting in March 1997) that the service was only funded for a total of six weeks - this could not be said to be raising false expectations.

4 (i) The AGO report noted that "an effective osteoporosis management service cannot be funded without access to bone densitometry" and suggested that a realistic number of DEXA scans would be 200 per 100,000 of population. The recommendations of the AGO report had been accepted by the NHS Executive. The rheumatologist took the view that the level of scanning provided by the service was approximately that recommended in the AGO report. Whilst the complainant might take the view that "... the impact of the company's actions could reasonably be expected to have an important impact on the Authority", both Merck Sharp & Dohme and the rheumatologist took the view that the impact was no greater than that of the recommendations already made by the NHS Executive to health authorities. The rheumatologist had written to the Health Authority indicating that he did not think that sufficient was being done by the Health Authority to implement the recommendations of the AGO report, as endorsed by the NHS Executive. He and Merck Sharp & Dohme had done no more than implement them, on a trial basis, to assess the need for the service in the Trust's area.

Also, the rheumatologist could not understand how the complainant was able accurately to assess "previous demand for bone densitometry ... as measured by referrals to NHS densitometry facilities". The rheumatologist had, for a number of years, been referring patients to densitometry services elsewhere in the NHS and also to private facilities. Given the Trust's status the invoices for these services were sent to the Trust direct and the rheumatologist therefore felt that the complainant might have had an unrealistic impression of the demand for the service.

Finally, the rheumatologist believed in any event that the real rate-limiting step in the rate of referrals for densitometry services was the distance which patients had historically had to travel to densitometry service providers, rather than real patient need. The service was an attempt to quantify this belief.

4 (ii) The service was neither "pump priming" nor intended to tie the Health Authority's hands. It was intended to allow the rheumatologist to demonstrate the level of demand to both the Trust and the Health Authority and thus argue for it to be given a higher priority. This was also made clear to general practitioners at the outset.

4 (iii) Merck Sharp & Dohme accepted that, ideally, patients scanned on a particular machine should be re-scanned on the same machine. However, Merck Sharp & Dohme would emphasise that, but for the service, the patients who were now being diagnosed as osteoporotic would not have been scanned at all. To suggest withholding the service from them entirely on the basis that they might have to be re-scanned on a different machine was something it found rather curious.

4 (iv) Merck Sharp & Dohme believed the complainant might have misunderstood its briefing document. Where relevant, it stated " ... A group of GPs should be identified who are interested in osteoporosis, will actively use guidelines and manage their patients accordingly and would value the service to the point where they would campaign for the Health Authority to support its availability.". It was quite clear that Merck Sharp & Dohme was not intending to "influence" anyone. One of the criteria for placement of the service was that there must be a cadre of GPs in the area who would genuinely value the service on a long term basis and would be willing to assist the lead specialist in using the results of the service to approach the health authority and request that it be made a funding priority. The GPs would be influenced by their pre-existing interest in the area and by the results of the service, not by any act of Merck Sharp & Dohme. To suggest that GPs in the Trust's area would be influenced by anything other than "... the perceived needs of patients" did them a serious disservice.

The complainant stated that "... it is not clear whether Merck Sharp & Dohme intended to acknowledge its involvement in the campaign." Merck Sharp & Dohme had some difficulty understanding this. Merck Sharp &

Dohme's financial involvement in the service was made perfectly clear by the rheumatologist at the launch meeting. The decision not to mention Merck Sharp & Dohme's involvement in the letter of invitation to the launch meeting was taken quite deliberately by the rheumatologist. He had made it clear to Merck Sharp & Dohme that he was keen not to be seen as too closely connected to any one pharmaceutical company, and Merck Sharp & Dohme respected that wish. Nevertheless, he made Merck Sharp & Dohme's involvement quite clear in open forum at the launch meeting. In any event, even had this involvement not been made plain, the Code allowed companies to associate their corporate name with the provision of a service under the supplementary information to Clause 18.1, but did not oblige them to do so.

Finally, Merck Sharp & Dohme should perhaps provide some details on the involvement of the marketing and sales departments in provision of the service in this case. The marketing department provided funding for the project and wrote the briefing document which was before the Appeal Board. The briefing document was the only briefing provided to the sales force in respect of this project. In addition, they assessed the proposal received from the representative to ensure it complied with all the criteria set out in the briefing document (not simply the product-related criteria).

The representative's involvement was limited to:

- proposing the rheumatologist as a potential provider for the service
- attending two meetings in January 1997 at which the logistics of the service were discussed; and
- supporting the PGEA-approved launch meeting at which a promotional stand was erected outside the meeting room (in accordance with usual practice at the postgraduate medical centre in question) and reasonable refreshment provided

The representative played no part in the selection of GP practices invited to use the service; in fact, the rheumatologist had invited every practice in the Trust's area to refer patients. The representative played no part in the writing or promulgation of the referral guidelines drawn up by the rheumatologist.

FURTHER COMMENTS FROM THE COMPLAINANT

1 The complainant found the first part of the response rather confusing; firstly saying that the company felt under no obligation to consult the Health Authority, secondly saying that the rheumatologist was responsible for doing this and thirdly implying that the company had informed the Health Authority after all. The point that the complainant would particularly like to make was that Merck Sharp & Dohme had experienced no difficulty in consulting the Health Authority about other closely related matters. For example, two colleagues in the public health department were consulted about the company's proposal to establish a bone densitometry research project looking selectively at patients from an Asian background. A meeting was held with Merck Sharp & Dohme in October 1996 about this matter, as a result of which advice was given to Merck Sharp & Dohme about obtaining ethical approval. More recently, another representative had been to see the complainant, to find out more about the Health Authority's strategies on heart disease and to inform him that Merck Sharp & Dohme was keen to be associated with Health Authority guidelines.

2 Two names given in Merck Sharp & Dohme's comments were incorrect. The formal consultation on the Health Authority's bone densitometry eligibility criteria was actually carried out by the complainant (by letter) in October 1996.

3 Merck Sharp & Dohme stated that one of its representatives did brief a colleague about the bone densitometry scheme in March 1997. Needless to say, the complainant had checked with him before making the appeal as the complainant was aware that he had been in contact with the company about the proposed research scheme and other matters. He had assured the complainant that he had not been given any details of the scheme which was the subject of the complaint. On seeing Merck Sharp & Dohme's letter, the complainant once again checked with his colleague who now recalled being told of a collaboration between the Trust and Merck Sharp & Dohme. He maintained that this was in vague terms only and that this was in no sense a formal attempt to inform the Health Authority or find out its views about the scheme. It was also notable that the reported date of this meeting with the Merck Sharp & Dohme representative was in March 1997. The service had already been fully planned by that stage and invitations to refer patients had been sent to general practitioners. It was around the same time that the complainant first telephoned the rheumatologist to raise his concerns.

4 Merck Sharp & Dohme said that it still had not seen a copy of the Health Authority guidelines on bone densitometry. A copy of the Health Authority paper setting out the eligibility criteria for bone densitometry had been sent to the Code of Practice Authority which, it was understood, had been relayed to the company. The complainant had also sent minutes of the relevant Health Authority meeting (November 1996) confirming that the eligibility criteria were adopted, after consultation with general practitioners and appropriate local consultants. The complainant believed that these minutes had also been relayed to Merck Sharp & Dohme.

If Merck Sharp & Dohme had consulted the Health Authority during the planning of its service it would have had access to these eligibility criteria. Unfortunately, it did not do so and this resulted in the circulation of different criteria, along with the rheumatologist's invitation to refer. Inevitably this would lead to confusion among general practitioners about the correct standards to use when referring for bone densitometry in future.

5 Merck Sharp & Dohme made a number of detailed criticisms relating to section 4 of the complainant's submission to the Appeal Board. The complainant did not feel it was necessary to answer these in detail, as the original evidence was strong, consistent and honest. It remained clear that the bone densitometry service represented a substantial investment by Merck Sharp & Dohme which was designed to have a major impact in one area of health care provision over the period of a year. This was expressly intended to influence the Health Authority's commissioning policy and yet the company's policy document made no reference to any need to

consult the Health Authority about this. This was a surprising and serious omission and formed the basis of the complaint that Merck Sharp & Dohme's actions in this case had brought discredit upon the pharmaceutical industry.

6 Merck Sharp & Dohme included extracts from the report of the Advisory Group on Osteoporosis and a recent NHS Executive circular on clinical effectiveness, as appendices to its letter. The complainant had followed up the latter document with its author and been assured that it was up to local health authority "managers to decide on the most appropriate service to provide, based on the clinical needs of the local population, taking into account the existing resources available".

The complainant considered that Merck Sharp & Dohme had attempted to interfere with a function which was properly that of the Health Authority; that was the assessment of clinical need and the setting of priorities. Indeed, the company appeared to have attempted to supplant the Health Authority in this role, at least on a temporary basis. This was made worse, in the complainant's opinion, by the failure of the company to explicitly acknowledge its role or intentions to the Health Authority.

The complainant was left to speculate at what stage in the process the company would have informed the Health Authority of the scale and nature of its involvement, and of its subsidiary work to identify general practitioners who would campaign for the continued local provision of bone densitometry services. What was clear, however, was the direct association between the company's investment in this scheme and its expectation of increased sales of Fosamax. Built into this expectation seemed to be a calculation that this increase would be at the expense of competitor products.

APPEAL BOARD RULING

The Appeal Board noted that the Health Authority guidelines referred to by both parties had been sent to Merck Sharp & Dohme at the end of August.

The Appeal Board noted that pharmaceutical industry sponsorship in the NHS was becoming more common. The Appeal Board considered that it was acceptable for the industry to undertake to provide such sponsorship as long as the arrangements were in accordance with the Code.

The Appeal Board considered that, in principle, the provision of a mobile bone densitometry service would enhance patient care and benefit the NHS. The service had to be provided in such a way as not to be an inducement to prescribe, supply, administer or buy any medicine.

The Appeal Board noted that the provision of the mobile bone densitometry service sought to increase both the number of patients diagnosed as osteoporotic and the use of Fosamax. The Appeal Board acknowledged that while other therapies could be prescribed, placement of the service was dependent on the participation of a local lead specialist who agreed that Fosamax should be used for the active management of patients in an area where there was a high potential for sales.

The Appeal Board noted Merck Sharp & Dohme's representatives' explanation concerning the use of the "Mobile Bone Densitometry Briefing Document" that it had been provided to regional managers for eliciting proposals regarding placement of the service. Merck Sharp & Dohme had said that representatives were told about the availability of the service by their regional manager and if one of their doctors was interested in the service, the representative could put forward a business case.

The Appeal Board noted that the briefing document clearly linked the provision of the mobile bone densitometry service with the promotion of Fosamax. Representatives were to be involved in the placement of the service. The Appeal Board considered it inevitable that representatives would be told that the company hoped to increase the local sales of Fosamax. The number of osteoporotic patients treated with Fosamax was one of three main outcomes of the service which would be measured.

In the Appeal Board's view, the briefing document associated the bone densitometry service with increased sales of Fosamax. The link between the two was clear. While there were other placement criteria to be satisfied the service was only provided to those specialists who agreed that Fosamax should be used for the active management of patients. The Appeal Board upheld the Panel's ruling of a breach of Clause 18.1.

The respondent's appeal therefore failed.

The Appeal Board noted that Merck Sharp & Dohme did not provide doctors using the mobile bone densitometry service with any supporting documentation. The doctors, therefore, did not receive any material which promoted Fosamax as a direct result of their using the service. The representatives were involved in proposing sites for the service but were not involved in the day to day running of the service. The Appeal Board acknowledged the complainant's views regarding Merck Sharp & Dohme's lack of consultation with the Health Authority but noted that the company had been in negotiation with a senior clinician and this should have been sufficient. Overall the Appeal Board did not consider that the arrangements for the implementation of the mobile bone densitometry service were such as to bring the industry into disrepute and so upheld the Panel's ruling of no breach of Clause 2.

The complainant's appeal therefore failed.

Complaint received **16 May 1997**

Case completed **1 October 1997**

CASE AUTH/553/5/97

GPs v NOVARTIS

Lamisil leaflet

Three general practitioners complained about a leaflet "Management of fungal infections of skin and nail". The practice had received seventeen copies of the leaflet. There was no indication of the sender but the leaflet did name a local consultant, a hospital and an NHS trust. The complainants established that Novartis, the manufacturers of Lamisil, had produced the leaflet as prescribing guidance with the support of the named consultant. Novartis said that the leaflet had been produced at local level by a representative. It had been mailed in error to general practitioners in the area.

The Panel noted that as the leaflet had been produced and distributed by one of Novartis' representatives and referred to Lamisil, it had to be regarded as promotional material.

The Panel ruled that the representative had failed to comply with the relevant requirements of the Code as prescribing information had been omitted and brand names of other companies had been used, most likely without prior permission. The Panel ruled that the use of the NHS trust logo and the multiple mailing meant that high standards had not been maintained. The Panel ruled that the distribution of the leaflet amounted to disguised promotion in breach of the Code. The Panel considered that the circumstances brought discredit upon, and reduced confidence in, the pharmaceutical industry and ruled a breach of Clause 2 of the Code.

Three general practitioners complained about a leaflet sent to the practice. The leaflet was entitled "Management of fungal infections of skin and nail". The front of the leaflet had the title followed by a named NHS Trust logo and the hospital name. This was followed by the name of a consultant. A treatment chart referred to a number of products by brand name including Daktarin, Canesten and Nizoral. The leaflet referred to Lamisil tablets, griseofluvin tablets, amorolfine lacquer and tioconazole solution in a chart comparing the costs of treating toe nail infection. A cost comparison of treating athlete's foot with Lamisil cream and clotrimazole cream was also included. In both of the cost comparisons the entry detailing the cost of Lamisil was highlighted. Lamisil was a product of Novartis Pharmaceuticals UK Ltd.

COMPLAINT

The complainants said that in March 1997, they had received the leaflet in their practice. The unusual feature of the mailing was that they received a total of seventeen copies of the leaflet addressed to each of the three partners. The envelopes, mailing labels or leaflets did not contain any indication of the sender's name or address nor any pharmaceutical company details or references to research etc, which usually accompanied mailings about medicinal products received in the practice.

The number of leaflets received surprised the complainants and they attempted to ascertain from whom and where the mailing had been sent. As the name of the local hospital and NHS trust, together with one of its consultants, appeared on the front of the leaflet, the complainants were concerned that NHS trust funding had been wasted on such a large mailing. The complainants contacted the secretary of the named consultant and were told that the consultant had not played any part in the sending out of this mailing, especially in the use of his name in the promotion. The secretary also advised that another practice had contacted her complaining that they had received twelve similar leaflets that day.

The complainants then contacted the manufacturer, Novartis Pharmaceuticals, at its head office. After leaving several messages, they spoke with somebody in the medical representatives department who requested a copy of the leaflet and promised to deal with the matter without delay.

Some weeks went by without hearing from the company. A message was left on 6 May and the call was returned on 7 May, stating that the matter was being investigated and that the complainants would be hearing from the company in due course.

On 15 May, the complainants received a telephone call from one of the regional sales managers apologising for the leaflet, the use of the logo and the consultant's name. She also apologised for the volume of copies received, which was due to a "serious administrative error". The complainants were told that a full apology would be coming in writing from the company. A copy of the letter of apology was supplied. The complainants said that when they had received the written reply, they were not happy with its contents or presentation. The reply did nothing to rectify the gross misrepresentation afforded to the GPs in the area.

The letter from the regional sales manager explained that the leaflet was produced by Novartis as prescribing guidance which had the support of the consultant. It should not have carried the trust logo and it was not a formal protocol agreed by the trust or the relevant health authority.

Due to a serious administrative error multiple copies of the leaflet were mailed to some GPs and for this an unreserved apology was given. The mailing was neither initiated nor implemented by anyone within the trust.

RESPONSE

Novartis explained that the leaflet on the management of fungal skin and nail infections was mailed to general practitioners in the particular area. The item in question was produced at a local level by a representative in association with a consultant. The leaflet was intended for use by the consultant to encourage rationalised prescribing for fungal infections within the area. It was not a promotional item for Lamisil (terbinafine) tablets or cream. It was not sponsored as such by the company or intended to be used for promotional purposes and would not therefore have carried prescribing information as specified in Clause 4.1 of the Code, or a declaration of

sponsorship as required by Clause 9.9.

Unfortunately, through an error of judgement on the part of the local representative, the leaflet was mailed to all general practitioners in the area via a local secretarial agency, without the consent of the consultant. This error was then confounded by the secretarial agency which instead of sending just one copy of the item to each of the address labels provided, used all of the labels at once causing multiple copies of the document to be sent to each of the general practitioners listed. This was not, however, a deliberate action of the type described and prohibited by Clause 12.2 of the Code in relation to frequency of mailing. The company understood that the leaflet was mailed in a conventional plain white envelope, with no associated materials.

The fact that this error had taken place was brought to the attention of Novartis by a manager at the hospital, who had been contacted by local general practitioners seeking an explanation for the multiple mailings they had received. The Novartis regional manager responsible for the representative involved immediately apologised profusely to the hospital and ensured that the consultant was informed of the error in case he too received any enquiries relating to the mailing.

In an attempt to correct the error, the regional manager put together a letter of apology, the text of which was submitted for approval by the manager at the hospital and the consultant, before being sent to each of the general practitioners identified as having contacted the hospital in relation to the mailing. Unfortunately, the complainants did not receive a copy of this letter until some time later, apparently because their point of contact with the hospital had been the consultant rather than the manager. By the time the complainants received a written apology, they had already contacted the company's head office a number of times. At this stage, the apology letter was clearly insufficient to apologise for the lack of response from the company, to explain why this mistake had occurred or to address the additional questions which had been raised in relation to the consultant's involvement with the mailing.

Novartis stated that the reasons for this lack of communication between head office and the regional managers charged with investigating this issue at a local level was currently being fully investigated. In addition, in the light of these events, a mailing had been sent to all representatives reminding them of their responsibilities under the Code in the context of involvement with mailings, however they may have originated.

Novartis offered its unreserved apologies again to the complainants for the inconvenience to which their practice had been put, both in receiving this unacceptable duplication of mailing and for the difficulties that thay had experienced in attempting to clarify the cause of these events.

Novartis reiterated that this was a localised event, confined to the particular area, and had occurred as the result of a number of errors both in judgement and execution, by one of the fieldforce. Having identified the errors every effort had been taken to apologise to all of the parties involved. Unfortunately, through an oversight, one of the practices was missed and, as a result, was not managed with the promptness and courtesy which they deserved from the company. This oversight was currently being fully investigated and a further letter of apology had been sent to the complainants.

PANEL RULING

The Panel noted that the leaflet had been produced and circulated by one of Novartis' representatives. It referred to Lamisil by brand name. It therefore had to be regarded as promotional material subject to the Code. In consequence certain requirements of the Code had not been met. For example the requirement for the inclusion of prescribing information. The brand names of other companies had been used, most likely without the prior permission of the owners. The Panel considered that the representative concerned had failed to comply with the relevant requirements of the Code. A breach of Clause 15.2 of the Code was ruled.

The Panel considered that the use of the NHS trust logo on the front of the leaflet was inexcusable. The use of the logo would ensure that the leaflet received attention from the recipients. The multiple mailing of the leaflet was unacceptable. The Panel considered that high standards had not been maintained and ruled a breach of Clause 9.1 of the Code. The Panel considered that the distribution of the leaflet amounted to disguised promotion and a breach Clause 10.1 of the Code was ruled.

The Panel considered that the circumstances were such as to amount to a breach of Clause 2 of the Code as they brought discredit upon and reduced confidence in the pharmaceutical industry and ruled accordingly.

Complaint received **21 May 1997**

Case completed **21 July 1997**

CASES AUTH/554/5/97 TO AUTH/560/5/97

GENERAL PRACTITIONER v ASTRA, EVANS MEDICAL, RHÔNE-POULENC RORER, PFIZER, NOVARTIS, ORGANON AND NAPP

Sponsorship of annual dinner

A general practitioner complained about the sponsorship of a dinner by Astra, Evans Medical, Rhône-Poulenc Rorer, Pfizer, Novartis, Organon and Napp. It was alleged that non-medical spouses, children, students, daughters, sons-in-law and politicians were present. The companies had had exhibition stands, which were attended by medical and non-member persons, in exchange for subsidising the dinner. There were no educational activities involved.

The Panel found that Rhône-Poulenc Rorer, Novartis, Organon and Napp had not been involved at all and were in consequence not in breach of the Code.

Astra, Evans Medical and Pfizer had all paid to have exhibition stands. The Panel did not consider that the event, which was the annual dinner of the Bangladesh Medical Association, had an educational content such as to justify support. Although there were to be speeches on various health related topics, these had been given to a mixed audience and had been no more than after-dinner speeches. The main purpose was a social event. In the view of the Panel, any form of support for such an event, whether by direct sponsorship or by sponsorship through the taking of an exhibition stand, was unacceptable in relation to the requirements of the Code and each of the three companies was ruled to be in breach.

COMPLAINT

A general practitioner complained that a number of pharmaceutical companies had breached the Code by sponsoring a Bangladesh Medical Association dinner held on 24 May, 1997, at the Sheraton Grand Hotel, Edinburgh. Non-medical spouses, children, students, daughters, sons-in-law and politicians were present.

The pharmaceutical companies only put out their stands, which were attended by medical and non-medical persons, in exchange for a big fat cheque to the Bangladesh Medical Association to subsidise the dinner. There were no educational activities involved under PGEA or CME.

Case AUTH/554/5/97 Astra Pharmaceuticals Limited

RESPONSE

Astra said that it did not sponsor the dinner. However, it did pay the Bangladesh Medical Association £550 for the exhibition of a promotional stand prior to the dinner commencing (exhibition 4-6pm, dinner 7pm onwards).

The dinner was followed by a medical discussion on health surveys and health promotion, positive education and health strategies in developing and non-developing countries and was, therefore, educational in nature. There were five speakers. The funding helped to cover the cost of room hire, stationery, mailing and travel and accommodation for speakers.

According to the Bangladesh Medical Association's records, 97 of the 172 attendees were doctors (a list was provided). The dinner was subsidised by the Association and all attendees had to pay £20-25 each (a copy of the invitation was provided). Astra's representative manned the stand and later attended the dinner. Astra confirmed that all the materials used at the exhibition were certified and pertained to Losec.

Given the situation, Astra did not believe that it had breached Clause 19.1 of the Code.

PANEL RULING

General principles The Panel accepted that fees for exhibition stands often subsidised the overall cost of a conference or a meeting etc. The amount paid had, however, to be reasonable for the exhibition facilities which were provided. Exhibition fees could not knowingly be used as a means of hidden subsidy for unacceptable activities. The overall arrangements for a meeting associated with an exhibition would have to comply with the requirements of Clause 19 of the Code. The meeting must have a clear educational content, any hospitality provided by a pharmaceutical company must be secondary to the nature of the meeting and must be appropriate and not out of proportion to the occasion. Hospitality must not be extended to spouses and others unless they qualified as delegates in their own right. Further, all materials had to comply with the Code and the exhibition should not be open to members of the public if promotional material for prescription only medicines was to be displayed.

In the present instance, the Panel did not consider that the annual dinner of the Bangladesh Medical Association had an educational content such as to justify support. Although there were to be speeches on various health related subjects, these had been given to a mixed audience and had been no more than after dinner speeches. The main purpose was a social event. According to the invitation, the cost for members was £20. Children and guests were allowed to attend. The charge for a guest was £25.

In the view of the Panel, any form of support for such an event, whether by direct sponsorship or by sponsorship through the taking of an exhibition stand, was unacceptable in relation to the requirements of the Code.

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The Panel ruled that Astra was in breach of Clause 19.1 of the Code.

Case AUTH/555/5/97 Evans Medical Limited

RESPONSE

Evans Medical said that it had been invited to participate in an exhibition prior to the 15th Annual Dinner of the Bangladesh Medical Association on the evening of 24 May. The invitation to exhibit was provided. The dinner was to be held at the Sheraton Hotel in Edinburgh and the contact was Evans' regional manager in Scotland. The fee for the stand was £400. The exhibition was to take place in the early evening separate from the dinner. Evans named two people who were to speak at the dinner. Evans understood that PGEA approval was sought. A list of other distinguished guests could be seen on the exhibition proposal. The exhibition fee was to be used to defray general administrative costs.

Evans' local representative and regional manager were in attendance for the exhibition. The exhibition was in a separate room to that where the dinner was to be held. Approximately 110 general practitioners, hospital doctors and trainees attended. Non-medical personnel were not allowed to visit Evans' stand, staff having been fully briefed on this issue. A range of products was displayed, all of the material having been approved through Evans' approval system. Its staff did not stay for the dinner. At no time was Evans involved with the invitation and nor did it lend its name to the event other than the exhibition.

In relation to the copy of the invitation to the dinner, Evans said that none of the companies exhibiting were mentioned and indeed no mention of the actual exhibition itself was made. The attendees had to pay £20 (subsidised) and guests £25. There was no statement that any pharmaceutical company was subsidising the meal. If there had been a direct association with the dinner, Evans would not have participated.

Evans believed it acted in good faith with regard to exhibiting at the event and that its staff conducted themselves according to the Code.

PANEL RULING

The Panel considered that the circumstances were the same as those in Case AUTH/554/5/97 and ruled that there had been a breach of Clause 19.1.

Case AUTH/556/5/97 Rhône-Poulenc Rorer Limited

Fisons was alleged to have breached the Code and the matter was taken up with Rhône-Poulenc Rorer Limited.

RESPONSE

Rhône-Poulenc Rorer stated that neither it, nor its affiliated company, Fisons plc, were involved in the dinner held on 24 May and no financial support was provided.

PANEL RULING

As neither Rhône-Poulenc Rorer nor its affiliate, Fisons plc, had been involved, the Panel ruled that there had been no breach of the Code.

Case AUTH/557/5/97 Pfizer Limited

Invicta was alleged to have breached the Code and the matter was taken up with Pfizer Limited

RESPONSE

Pfizer denied any contravention of the Code because its involvement with the dinner and the preceding pharmaceutical exhibition was in compliance with its provisions.

In April 1997 the company's representive covering Glasgow was approached by a member of the Bangladesh Medical Association concerning potential sponsorship for a meeting organised by the Association. The meeting was described as the Annual Dinner of the Association and would consist of a pharmaceutical exhibition, a dinner and after-dinner speeches on medical issues. It was explained by the Bangladesh Medical Association member that the exhibition would begin at 4pm on 24 May and would last for approximately four hours. Dinner was to be served at 8pm. It was further explained that the expected audience would consist mainly of general practitioners and hospital doctors and that there would be specially invited guests who would be senior medical figures within Scotland and the UK (a list of names was provided). The company's representative was not shown the invitation leaflet, which only came to Pfizer's attention when the Authority sent it a copy, and had advised that the attendance of non-medical personnel was not mentioned.

Pfizer agreed to erect a promotional stand at the exhibition for which it would contribute £150. Pfizer believed that this level of funding was appropriate for such a stand and pointed out that this funding would only cover a very small part of the total cost of the event. The letter of complaint referred to the companies sponsoring the Bangladesh Medical Association dinner. Pfizer sponsorship related to the entire function, including the pharmaceutical exhibition prior to the dinner and the subsequent speeches on medical issues.

A separate function room was provided within the hotel for the pharmaceutical exhibition, which was not open to the public. Pfizer's representatives had advised that approximately 200 people visited the exhibition and this was consistent with the expected attendance of over 200 doctors. An attendance list of the delegates was not circulated to either Pfizer or any of the other exhibiting companies and the delegates were not supplied with name badges.

During the exhibition, the company's representatives became aware that non-medial guests would be attending the dinner but they were not aware of any non-medical personnel visiting the exhibition apart from a small number of children who were seen in the function room accompanied by adults. No material or promotional items were distributed outside of the separate function room and Pfizer's' representatives did not distribute any such items to any individuals who to their knowledge were not medical personnel. The materials on the Pfizer stand consisted only of promotional material for Pfizer products.

At 7pm the Pfizer exhibition stand was dismantled as it was believed that the majority of doctors had visited the

stand. Neither of the company's representatives attended the dinner which was due to be served at 8pm. Both the company's representatives left the hotel at approximately 7.15pm as their involvement was only relevant to the exhibition.

The after-dinner speeches were supposed to be upon various medical and health subjects, a representation upon which the Pfizer representatives relied. The seniority and profile of the "special guests" also indicated that this was a reputable medical gathering which would be addressed with relevant speeches on medical issues.

The involvement of the company's representatives did not proceed further than the provision of the exhibition stand. At no time was a meal or other function involving non-medically qualified spouses or families of members of the Bangladesh Medical Association attended by the Pfizer representatives. Although it was not known exactly how the sum paid by sponsorship was spent, in Pfizer's opinion the sum was well within the bounds of an acceptable contribution towards sponsorship of such a function involving a pharmaceutical exhibition of four hours' duration and speeches of an educational nature.

PANEL RULING

The Panel considered that the circumstances were similar to those in Case AUTH/554/5/97 and ruled that there had been a breach of Clause 19.1.

Case AUTH/558/5/97 Novartis Pharmaceuticals (UK) Ltd

RESPONSE

Novartis confirmed that the Bangladesh Medical Association had contacted the company for corporate sponsorship for its meeting, but this had been declined and the invitation had been forwarded to the Authority for information in view of its questionable nature. Investigation had shown that this meeting was not sponsored by any head office personnel and no payments had been authorised by the company in relation to this meeting.

It appeared that members of the Bangladesh Medical Association also contacted Novartis field based representatives in the Edinburgh area requesting a £500 donation for the meeting. This request was declined because this meeting was known to be a purely social event to which non-health professionals would be invited. It had not been possible to identify any sponsorship of this group by the Novartis field force and nor had any authorised payment to the Bangladesh Medical Association been identified.

Attempts had been made to clarify any possible involvement with this meeting both with the Bangladesh Medical Association and the meeting venue but this had proved non-productive.

In conclusion, Norvatis' investigations had been unable to identify any payment to the Bangladesh Medical Association by the company and it therefore concluded that the meeting was not sponsored by Norvatis as suggested by the complainant.

PANEL RULING

As there was no evidence that Norvatis had been involved, the Panel ruled that there had been no breach of the Code.

Case AUTH/559/5/97 Organon Laboratories Ltd

RESPONSE

Organon said that it could categorically advise that no-one from Organon had been involved with this dinner. Organon was not present and nor had it any involvement in sponsorship. The matter had been checked with the sales and marketing staff and with accounts, and no contribution to the Association had been made by Organon.

PANEL RULING

As Organon had not been involved, the Panel ruled that there had been no breach of the Code.

Case AUTH/560/5/97 Napp Laboratories Limited

RESPONSE

Napp said that its internal enquiries had revealed that it had no involvement with the Annual Dinner of the Bangladesh Medical Association. It did not provide any contribution to the event, financial or otherwise, and nor did any of its representatives attend the dinner. Napp had confirmed this by contacting the representatives of the Bangladesh Medical Association who organised the event.

Napp noted that the invitation enclosed by the complainant did not contain any evidence of sponsorship by Napp or any other pharmaceutical company. Napp was confident that it had no involvement.

PANEL RULING

As Napp had not been involved, the Panel ruled that there had been no breach of the Code.

Complaint received **28 May 1997**

Cases completed **17 July 1997**

DIRECTOR/MEDIA v EISAI and PFIZER

Promotion of Aricept

A letter in the British Medical Journal critical of the promotion of Aricept by Eisai and Pfizer was taken up as a complaint under the Code of Practice in accordance with established procedure. The complainant said that the statement in the advertisement "Mum has Alzheimer's but she knew I was calling today", and the related photographs, implied that in patients with Alzheimer's disease treatment with Aricept (donepezil) would improve function enough to have a measurable impact on the carer's mood. As far as the complainant was aware there had been one published randomised control trial of the use of donepezil in Alzheimer's disease and this showed no improvement in the quality of life for carers. The advertisement suggested an unrealistic improvement in the mental status of patients.

The Panel noted that Aricept was licensed for the symptomatic treatment of mild or moderate dementia in Alzheimer's disease. The Panel did not accept the allegation that the advertisement suggested an unrealistic improvement in the mental state of the patient and no breach of the Code was ruled in that regard. The Panel did not accept that the photographs implied that Aricept would have a positive effect on a carer's mood. They simply portrayed a natural reaction between mother and daughter. The Panel considered the photographs were reasonable and not misleading in terms of any implied claim for Aricept. No breach of the Code was ruled.

A letter in the British Medical Journal, 24 May 1997, from a senior lecturer in public health medicine, criticised the promotion of Aricept. The advertisement in question, which appeared on a wrapper around the British Medical Journal (BMJ), was headed "Mum has Alzheimer's" beneath which was a large colour photograph of an elderly woman and her daughter, both smiling. Partially superimposed in the top right hand corner of this photograph was another, much smaller, sepia photograph of the daughter looking worried. Beneath the large photograph was the phrase, which ran on from the heading, "but she knew I was calling today". The advertisement was jointly issued by Eisai Ltd and Pfizer Limited.

COMPLAINT

The complainant was angry and concerned that advertising space on the wrapper around the clinical research edition of the BMJ (issues of 3 and 10 May) was sold to promote donepezil hydrochloride (Aricept). This was the first time that the complainant had been aware of a promotion of this nature and she found this form of advertising disturbing. While the complainant appreciated that the BMJ generated necessary income from pharmaceutical companies and she could deal with advertisements within the journal, she found that to be faced by a paper strip on top of the BMJ that had to be forcefully removed before one could even read the contents page was irritating and intrusive. No doubt because of this, it was a successful marketing ploy and generated enormous amounts of income. As a general policy, however, the complainant hoped that the journal would reconsider accepting this type of advertisement, as she was sure she was not alone in finding it offensive.

The complainant pointed out that the BMJ had taken great strides in supporting a critical and rational use of the evidence base in medicine. What policy was adopted in scrutinising the content of advertisements placed in the BMJ? The promotion for donepezil - "Mum has Alzheimer's but she knew I was calling today" and the related photographs, implied that in patients with Alzheimer's disease treatment with the medicine would improve function enough to have a measurable impact on the carer's mood. As far as the complainant was aware there had been one published randomised controlled trial of the use of donepezil in Alzheimer's disease, and this showed no improvement in the quality of life of carers. The advertisement suggested an unrealistic improvement in the mental status of patients.

* * * *

The Authority informed the complainant and the companies that the criticism regarding the lack of data to show an improvement in the quality of life of carers and the suggested unrealistic improvement in the mental status of patients were being dealt with under the Code. The criticism concerning the use of the "wrapper" as an advertisement was not taken up as a matter under the Code as the principle of using such advertisements was not prohibited by the Code. The Editor of the BMJ had in fact responded to this point in a published footnote.

RESPONSES

Case AUTH/561/5/97

Eisai submitted that the complainant was mistaken as to the claim it was making for Aricept. The principal claim made by the advertisement was the improvement in cognitive function of the patient, rather than in the quality of life of the care-giver. This claim was supported by the summary of product characteristics (SPC) and two pivotal phase III studies.

The SPC stated that: "In two double-blind randomised trials, statistically significant drug placebo differences were present for each of the two primary outcome measures (ADAS-cog/CIBIC plus)". The ADAS-cog scale was one of the most widely used measures of cognition in major therapeutic trials of Alzheimer's disease.

Study 301 showed a statistically significant improvement in ADAS-cog measures over the 12 week treatment period. It showed loss of treatment effect during the placebo washout phase. Study 302, which had been accepted for publication in Neurology, showed a statistically significant improvement in ADAS-cog over the 24 week study period and again the washout period provided evidence of treatment effect.

In the phase III studies, the quality of life of the care-giver

was not an efficacy end-point. As secondary efficacy variables, patient quality of life was assessed although the studies were not designed to show statistical differences between treatment groups. In both studies, 301 and 302, patient quality of life measurements did not show statistically significant differences between the groups.

Eisai submitted that the photograph and wording were not intended to, and did not, claim or imply an improved quality of life of the care-giver. An issue incidental to the message conveyed by the advertisement which concentrated on the patient's condition. The photograph showed that a daughter (who was not even necessarily the primary care-giver) was pleased that her mother's condition had been improved by her new medication. Eisai submitted that this was a natural and self-evident reaction and did not require specific substantiation. It was fair to reflect the daughter's happy mood in the photograph this way.

Eisai submitted that the advertisement was fair and not misleading in any way, and that the claim actually made (as opposed to that which had been inferred) was capable of substantiation and was therefore in conformity with Clauses 7.2 and 7.3 of the Code.

Case AUTH/562/5/97

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

PANEL RULING

The Panel noted that Aricept was licensed for the symptomatic treatment of mild or moderate dementia in Alzheimer's disease. It was perfectly reasonable for it to be promoted to healthcare professionals. The Panel did not accept the allegation that the advertisement suggested an unrealistic improvement in the mental state of the patient. No breach of Clauses 7.2 and 7.3 was ruled.

The Panel noted that the two photographs in the advertisement portrayed, in the small photograph, a daughter looking worried about her mother's condition and, in the large photograph, the daughter and mother both looking pleased.

The copy above the photograph stated "Mum has Alzheimer's" with the statement "but she knew I was calling today" appearing beneath the large photograph. The Panel considered that the daughter might not be the primary carer. The Panel did not accept that the photographs implied that Aricept would have a positive effect on a carer's mood. The photographs simply portrayed a natural reaction between mother and daughter. The Panel considered that the photographs were reasonable and were not misleading in terms of any implied claim for Aricept. No breach of Clause 7.2 of the Code was ruled.

Proceedings commenced **30 May 1997**

Cases completed **25 July 1997**

CASE AUTH/563/5/97

MERCK SHARP & DOHME v PROCTER & GAMBLE

Promotion of Didronel PMO

Merck Sharp & Dohme submitted a complaint about two journal advertisements and a leavepiece for Didronel PMO issued by Procter & Gamble.

Merck Sharp & Dohme alleged that the claim for long-term fracture reduction intimated in the first of the two advertisements placed undue emphasis on non-significant data. In relation to the leavepiece, it was alleged that the claim "During 5 years of therapy the previously observed 63% reduction in vertebral fracture rate in the cyclical etidronate group was maintained" and the presentation of fracture data in the bar chart were misleading. It was also alleged that the claim "No other bisphosphonate can offer you such long-term assurance. The incidence of adverse events with cyclical etidronate in this study were comparable to control" could not be substantiated.

The Panel considered that readers of the advertisements would have no doubt that the data regarding vertebral fracture rate was only trend data. Five year data on bone mass lent support to the trend data on fracture rate and put the latter into context. In the Panel's view neither advertisement placed undue emphasis on non-significant data and no breach was ruled.

In relation to the leavepiece, the Panel considered that the bar chart clearly showed placebo results for only years 0 - 3 and, in the Panel's view, readers would appreciate that there was no placebo group in years 4 - 5. Given the context, the Panel considered that neither the claim nor the associated bar chart were misleading and no breach was ruled. In relation to the claim "No other bisphosphonate can offer you such long-term reassurance. The incidence of adverse events with cyclical etidronate in this study were comparable to control" the Panel considered this would be taken to mean that this was so throughout the five years of the study. It was not so as the second phase of the study, years 4 - 5, was not placebo controlled and so the incidence of adverse events could not be compared with control at that time. The Panel considered that the claim was not capable of substantiation and ruled a breach of the Code.

Merck Sharp & Dohme Limited complained about the promotion of Didronel PMO (etidronate disodium/calcium carbonate) by Procter & Gamble Pharmaceuticals.

The items at issue were two journal advertisements each referenced D826a and a leavepiece referenced D836b.

A JOURNAL ADVERTISEMENT

The advertisements appeared on successive right hand pages of "Hospital Doctor" 17 April 1997. The first advertisement featured a flash of lightning with the heading "Osteoporotic fractures may strike again and again. The threat is frightening but the long-term forecast is bright." The second advertisement featured three female statues one of which was being restored by workmen and another was being struck by lightning. This advertisement was headed "With Didronel PMO, you can achieve outstanding results for years to come." In the bottom left hand corner was a box of text headed "New long-term data". The efficacy data within this box referred to recent data which had shown a trend towards a progressive reduction in vertebral fracture rate during years 6 and 7 of treatment.

1 Use of trend data

COMPLAINT

Merck Sharp & Dohme alleged that the claim of long term fracture reduction intimated on the first advertisement had only been substantiated on the basis of trend data. This data was contained within the box on the second advertisement. Indeed, great emphasis was placed on this data with the claim "This trend indicates that 98% of patients did not have a new vertebral fracture during the 6th and 7th year of treatment." Merck Sharp & Dohme alleged that the use of the word "trend" did not suffice to make it clear to the reader that the data was not statistically significant; indeed, the Watts abstract on which the claim was based made no mention of statistical testing for vertebral fracture incidence. Merck Sharp & Dohme alleged that this claim placed undue emphasis on non-significant data and thus was in breach of Clause 7.2 of the Code.

RESPONSE

Procter & Gamble did not accept that there was anything improper in its use of the claim "Osteoporotic fractures may strike again and again. The threat is frightening but the long term forecast is bright."

Procter & Gamble said that Merck Sharp & Dohme was incorrect to state that this claim was supported only by vertebral fracture reduction trend data (derived from the Watts seven year study). It was clear from the highlighted box on the second advertisement that Procter & Gamble also referred to long-term bone mass density data taken from the Storm 1996, Miller 1995 and Watts 1995 studies. Copies of these papers were provided. As was clear from the references, these data were statistically significant:

Study	Vertebral bone mass (% change from baseline)
Storm	+6.9% vs baseline at year 5 (significant)
Miller	+12.5% vs baseline at year 7 (significant)
Watts	+ 8% vs baseline at year 7 (significant)

Procter & Gamble said that bisphosphonates were very widely used in the treatment of osteoporosis to inhibit bone resorption which led to an increase in bone mass generally. In the treatment of osteoporosis, bone mass density data were widely accepted as supportive of, and often a surrogate endpoint for, fracture incidence data, on the basis that an increase in bone mass density would be supported by a decrease in fracture incidence. Previously published studies involving Didronel PMO had demonstrated that a statistically significant increase in vertebral bone mass density was associated with a

statistically significant decrease in the rate of vertebral fractures; for example, studies by Storm 1990 and Watts 1990. It was the totality of the data available (endorsed by the extension of the Didronel PMO licence last year to long term use) which fully justified the conclusion that the "forecast" for patients was "bright".

Procter & Gamble referred to its use of fracture trend data derived from Watts 1995. While the company accepted that the vertebral fracture data derived from this abstract was trend data, it was the company's understanding that the use of such data was not prohibited by the Code. The supplementary information to Clause 7.2 emphasised that care must be taken in the presentation of all statistical information and that differences not reaching statistical significance must not be presented in such a way as to mislead. Procter & Gamble said that it had complied with this provision. It should be noted that it only used that data to support the claim made in the highlighted box. Moreover, the company had ensured that it had used the words "trend" and "trend towards" in the two consecutive sentences which were the only places referring to the vertebral fracture results from the Watts study.

Procter & Gamble submitted that this data was of scientific interest and relevance to doctors and it defended its right to refer to the data in the qualified and careful manner in which it had. The company believed that, given the fact that the data did not stand alone and must be viewed in the context of bone mass density data for the product and the class as a whole, the use of the data could not reasonably be said to mislead as to the efficacy profile of cyclical etidronate.

Procter & Gamble submitted that Merck Sharp & Dohme was incorrect in saying that the data was not significant. The 98% figure was calculated by subtracting from 100% the 2% of patients who had taken cyclical etidronate for 7 years and suffered vertebral fractures. While it was correct that the Watts abstract did not mention statistical testing, Procter & Gamble had carried out its own statistical analysis of the figures and had calculated that both the trend in fracture incidence and fracture rate data were significant (p=0.01 and p=0.001 respectively). However, since this analysis did not appear in the publication and was derived from trend data, Procter & Gamble did not refer to it in the advertisement. Procter & Gamble considered that this illustrated the conservative approach which it had taken in the presentation of the data from the study.

In the circumstances, Procter & Gamble considered that it had not placed undue emphasis upon non-significant data and strongly rejected the allegation that it was in breach of Clause 7.2.

PANEL RULING

The Panel first noted that the advertisements in question had to be considered as two separate advertisements and not a two page advertisement as they appeared on successive right hand pages with intervening material. This was in accordance with the supplementary information to Clause 6 of the Code.

The Panel noted that long term bone mass density data was generally accepted as at least supportive of fracture incidence data. The long term bone mass density data from studies by Storm 1996, Miller 1995 and Watts 1995 were all statistically significant from baseline at either 5 years (Storm) or 7 years (Miller and Watts). The trend data (Watts 1996) was from a follow on study to a 5 year study. Patients who had completed the 5 year study were randomised to receive either cyclical etidronate or placebo for a further 2 years. In a group of 42 patients who had received cyclical etidronate for 7 years, only one patient suffered a vertebral fracture during the 6th and 7th year of treatment. Thus 98% of patients remained fracture free. The Panel noted that no statistical data were given in the publication, Procter & Gamble had submitted that the trends in both fracture incidence and fracture rate were significant.

The Panel noted that the use of trend data *per se* was not necessarily in breach of the Code. It was a question of how such data had been used. The supplementary information to Clause 7.2, statistical information, stated that "Differences which do not reach statistical significance must not be presented in such a way as to mislead".

The Panel noted that the box on the second advertisement contained two columns of text. The first column of text described the proven increased vertebral bone mass seen with cyclical etidronate and then referred to the trend towards progressive reduction in vertebral fracture rate during years 6 and 7. The Panel considered that the proven 5 year data on bone mass lent support to the trend data on fracture rate and put the latter into context. The Panel noted that the text quite clearly referred to trend data. The Panel considered that readers of the advertisement would have no doubt that the data regarding vertebral fracture rate was only trend data. In the Panel's view neither advertisement placed undue emphasis on non-significant data. No breach of Clause 7.2 was ruled.

B LEAVEPIECE

The four page A4 leavepiece (D836b), which bore similar illustrations to the second journal advertisement, referred to detailed data from a study, "Five years of clinical experience with intermittent cyclical etidronate for postmenopausal osteoporosis", Storm *et al* (1996). It had also been mailed to a number of hospital doctors.

2 Reduction in vertebral fracture rate

Page 2 of the leavepiece was headed "The 5 year study" and under the heading "The study" described it as a 2 year limited open-label follow-up study of postmenopausal women from the initial 3 year study. Beneath the heading "The results" was the claim "During 5 years of therapy the previously observed 63% reduction in vertebral fracture rate in the cyclical etidronate group was maintained." Beneath this claim was a bar chart showing vertebral fracture rates in years 0-3 for placebo and cyclical etidronate and in years 4-5 for cyclical etidronate.

COMPLAINT

Merck Sharp & Dohme alleged that both the claim "During 5 years of therapy the previously observed 63%

reduction in vertebral fracture rate in the cyclical etidronate group was maintained" and the presentation of fracture data in the bar chart were misleading and in breach of Clause 7.2. As there was no placebo group in years 4-5 it was not possible to state that a given reduction in fracture rate was "maintained". A more appropriate phrase might be that the fracture rate in the cyclical etidronate group was unchanged over a further two years of open label therapy.

RESPONSE

Procter & Gamble stated that the claim was, in fact, taken directly from the abstract and the discussion section of this peer-reviewed paper. The claim referred to the fact that a similar reduction in the vertebral fracture rate was observed during years 0-3 (Study 1, the principal study) (38 fractures per 100 patient years) and in the two years of open label follow up. Indeed, the fracture rate actually reduced slightly to a rate of 33 per 100 patient years during Study II (years 4-5).

Procter & Gamble said that in the conclusion paragraph of the abstract the author had stated "... the previously observed reduction in vertebral fracture rate in the etidronate group is maintained during at least 5 years of therapy". The discussion section stated "In the former etidronate group, continued therapy maintained the low incidence of vertebral fractures and low fracture rate observed in Study 1".

Procter & Gamble referred to Merck Sharp & Dohme's objection to the word "maintained" and its suggestion to use "was unchanged". Instead, Procter & Gamble considered that the most accurate way to ensure that the views of an author were represented clearly was to use his words. The company did this in choosing to use the word "maintained." Procter & Gamble challenged Merck Sharp & Dohme's opinion that its alternative had any actual difference in meaning, since the author also stated in the results paragraph of the abstract that: "the fracture rate in the former etidronate group was unchanged." This suggested that he regarded the words as interchangeable.

Procter & Gamble pointed out that both the claim at issue and the bar chart representing the data from the study appeared under a heading which stated that this was a "limited open-label follow-up". Immediately underneath the bar chart appeared the statement: "Fracture rate for all vertebral fractures in the cyclical etidronate group was significantly lower than placebo in years 0-3 ($p<0.05$). This fracture rate was reduced in the cyclical etidronate group (not significant) over years 4-5." Procter & Gamble considered that it spelled out very clearly the parameters of the study and the circumstances in which the results arose.

In the light of the above, Procter & Gamble considered that it had accurately reflected the true meaning of the conclusions drawn by the author in this paper and represented those results fairly and without any misrepresentation. It was completely contrived to suggest that doctors would be misled as to the efficacy profile of the product in this regard.

PANEL RULING

The Panel noted the submission from Procter & Gamble regarding the use of the study author's words. The Panel noted that under the Code companies were required to ensure that the use of quotations etc were not in breach of the Code. It was not acceptable to use the author's words if such use would contravene the Code.

The Panel noted that the 5 year data being presented had come from an initial placebo controlled 3 year study of treatment with etidronate which had been followed by a further 2 year open label study of etidronate. There was thus no placebo control group for years 4-5.

The Panel noted that the bar chart consisted of 3 bars. For years 0-3 there were two bars, one tall grey bar marked "placebo" and one smaller purple and blue bar marked "cyclical etidronate". The bars denoted all vertebral fractures (rate per 100 patient years). There was a large difference in the height of the placebo bar and the etidronate bar which was marked with a double ended arrow above the etidronate bar and labelled "63%" followed by an asterisk. For years 4-5 there was only a purple and blue bar shown for etidronate. The height of the etidronate bar in years 4-5 was a little less than that shown for years 0-3. There was no double headed arrow over the etidronate bar for years 4-5 and no placebo results were given for years 4-5. The asterisk was explained below the bar chart by the statement "Fracture rate for all vertebral fractures in the cyclical etidronate group was significantly lower than placebo in years 0-3 ($p<0.05$). This fracture rate was reduced in the cyclical etidronate group (not significant) over years 4-5.".

The Panel considered that the bar chart clearly showed placebo results only for years 0-3. In the Panel's view readers would appreciate that there was no placebo group in years 4-5. The Panel noted that the double headed arrow emphasising a 63% reduction in vertebral fracture rate only appeared over the etidronate bar for years 0-3, during the time when the study had been placebo controlled. The bar for etidronate in years 4-5 was a little smaller than that for years 0-3. The Panel considered that given their context neither the claim "During 5 years of therapy the previously observed 63% reduction in vertebral fracture rate in the cyclical etidronate group was maintained" nor the associated bar chart were misleading as alleged. No breach of Clause 7.2 of the Code was ruled.

3 Tolerability data

COMPLAINT

Merck Sharp & Dohme referred to the claim on page 3 of the leavepiece that "No other bisphosphonate can offer you such long-term reassurance. The incidence of adverse events with cyclical etidronate in this study were comparable to control." Merck Sharp & Dohme said that the claim implied use of a control group for the full five years. However, the reference described a placebo group only for years 0-3 and therefore could not support the claim made. The company stated that it would be preferable to state that the adverse event rate was comparable to control during the three year control period. The claim as it stood could not be substantiated in breach of Clause 7.3 of the Code.

RESPONSE

Procter & Gamble submitted that with regard to the first

part of the claim at issue, extensive clinical experience and 19 years of postmarketing surveillance had shown etidronate to have an excellent safety profile. This was supported both by Procter & Gamble's own database (2.3 million patient years of exposure to etidronate for osteoporosis treatment alone, worldwide) and also the results of the various clinical trials which had been carried out involving etidronate. Procter & Gamble said that no other bisphosphonate could claim such extensive international clinical experience - which was an issue of interest to doctors - and certainly not Merck Sharp & Dohme's alendronate which was only launched relatively recently and had already been the subject of further instructions for use consequent upon early postmarketing surveillance.

Recently, van Staa (1996) summarised the interim results of a cohort epidemiological study of 8000 patients taking etidronate in the UK and concluded that, when compared to an age and gender matched osteoporotic control group (n=8000) and a non-osteoporotic control group (n=8000), neither of which had taken etidronate, there was no increased risk of any type of upper gastrointestinal event. These were the most common type of adverse event to be associated with bisphosphonates, especially amino-bisphosphonates such as Merck Sharp & Dohme's product alendronate.

Further, etidronate was the only bisphosphonate upon which there was data relating to the effects of continuing treatment for osteoporosis for a period of five years or over. In addition to the Storm study 1996, Miller 1995 observed the effect of treatment for seven years and concluded that etidronate "is safe and well tolerated and does not cause osteomalacia".

Procter & Gamble submitted that with regard to the Storm study 1996 and the second part of the claim "The incidence of adverse events with cyclical etidronate in this study were comparable to control", it had reflected very closely the conclusions of the author, who stated that "no adverse event reported during the study was considered to be related to the study treatment" and in the discussion that "intermittent cyclical treatment with etidronate is safe and well tolerated over a period of more than 5 years of treatment". Although it was the case that a control group was not used during the final two open years, it was clear that the author considered that the existence or otherwise of such a control group would not have made any difference to the results he observed. Since there were no adverse events reported which were related to the study treatment, specific control group, or historical control group, data could only have improved the comparative event profile with treatment still further.

Procter & Gamble submitted that it was certainly able to make the claim that the incidence of adverse events was comparable to control in this study. Merck Sharp & Dohme's contention that it would have been "preferable" expressly to raise a comparison between 5 year treatment group data and 3 year control group data, besides suggesting that the company itself saw this as a marginal issue of judgement, would have conveyed a confusing message to doctors that would mislead as to the reasonable conclusion to draw as to the safety profile of the product. Procter & Gamble strongly contested that it had made a claim incapable of substantiation in breach of Clause 7.3 of the Code.

PANEL RULING

The Panel considered that, given its context, the claim "The incidence of adverse events with cyclical etidronate in this study were comparable with control" would be taken to mean that this was so throughout the five years of the study. This was not so. The second phase of the study (years 4-5) was not placebo controlled, and so the incidence of adverse events could not be compared with control at this time. The Panel considered that the claim was not capable of substantiation as alleged and ruled a breach of Clause 7.3 of the Code.

Complaint received **2 June 1997**

Case completed **30 July 1997**

CASE AUTH/564/6/97

DIRECTOR/SCRUTINY v GLAXO WELLCOME

Legibility of prescribing information

It was considered during the course of the routine scrutiny of journal advertisements that the prescribing information in an advertisement for Imigran 50 was illegible.

This was not accepted by Glaxo Wellcome and the matter was accordingly referred to the Code of Practice Panel as a complaint. The Panel did not consider that the prescribing information could easily be read and a breach of the Code was ruled.

This case arose from the routine scrutiny of journal advertisements. As the matter could not be settled, it was referred to the Code of Practice Panel as a case in accordance with Paragraph 17.4 of the Constitution and Procedure.

The advertisement in question was for Imigran 50 issued by Glaxo Wellcome UK Limited which had appeared in Doctor, 3 April 1997. The prescribing information was in white against a dark background and appeared in columnar form down the left had side of the advertisement.

COMPLAINT

It had been considered during the course of routine scrutiny of journal advertisements that the prescribing information was illegible and that the advertisement was accordingly in breach of Clause 4.1 of the Code.

RESPONSE

Glaxo Wellcome said that having reviewed the prescribing information on the original copy, it was of the opinion that the advertisement did not breach Clause 4.1 by virtue of its legibility. Certainly it could be read without difficulty by a random group who were asked to comment, including an ageing medical director.

The type size and font fell within that specified in the supplementary information of the Code, as did the line length. Sufficient space between the lines was present and the type style was one that was easily read. The supplementary information to Clause 4.1 preferred, but did not stipulate, dark print on a light background but the contrast here was sufficient to make the text clear.

Overall legibility was a subjective assessment of the whole of the prescribing information, but, based upon the above parameters and a review of the advertisement itself, Glaxo Wellcome was of the opinion that the information presented in the original advertisement was clear and legible and fulfilled the requirements of Clause 4.1.

PANEL RULING

The Panel considered that the combination of type size and the fact that the text was in white against a dark background was not conducive to ready reading of the prescribing information. It was at the outer limits of legibility. When white was used on a dark background a larger and more prominent type face was needed to ensure clarity than was the case with black print on a white background. The Panel noted a similar advertisement two pages on in the same issue of the journal which was, if anything, even more difficult to read.

Clause 4.1 of the Code stated that "The prescribing information listed in Clause 4.2 must be provided in a clear and legible manner .....". The Panel did not consider that the test was whether the prescribing information could be read at all but whether it could easily be read. The Panel did not consider that the prescribing information could easily be read and ruled a breach of Clause 4.1.

Proceedings commenced **16 May 1997**

Case completed **25 June 1997**

CASE AUTH/566/6/97 *NO BREACH OF THE CODE*

HOSPITAL PHARMACIST v RHÔNE-POULENC RORER

Advance notification letter on Clexane

A hospital information pharmacist complained that a letter concerning an anticipated new indication for Clexane (enoxaparin) issued by Rhône-Poulenc Rorer referred to the ESSENCE study (Efficacy and Safety Study of Enoxaparin in Non-Q-wave Coronary Events) but that the company had not supplied him with a copy of the study, contrary to the requirements of the Code, when requested to do so, the explanation being that it had not yet been published. A congress report briefly summarising the study had been sent to him and later on the complainant had been sent a more extensive abstract.

The Panel noted that companies were required to provide substantiation for information, claims and comparisons without delay at the request of a member of a health profession. The Panel noted that although the complainant had not been supplied with the study itself, he had been sent relevant data both in the congress report and in the study abstract. In the Panel's view, the information provided was sufficient to meet the requirement that substantiation be provided on request. No breach of the Code was ruled.

A hospital principal pharmacist complained about a "Dear Pharmacist" letter on Clexane sent by Rhône-Poulenc Rorer Limited. The letter in question was headed "Enoxaparin (Clexane) in Unstable Angina/Non-Q-Wave MI - Financial Planning Information". The letter referred to a study concerning enoxaparin in unstable angina/non-Q-wave MI (myocardial infarction) and stated that a licence was anticipated during the next NHS financial year. The product was currently licensed in the UK for the prevention and treatment of deep vein thrombosis and the prevention of thrombus formation during haemodialysis.

The letter included a number of calculations comparing the costs of treating unstable angina/non-Q-wave MI with enoxaparin compared with intravenous infusion of unfractionated heparin. One of the references in the letter was to the ESSENCE study (Efficacy and Safety Study of Enoxaparin in Non-Q-wave Coronary Events). The letter was signed by the product manager and by a senior physician and was dated April 1997.

COMPLAINT

The complainant had received the letter from Rhône-Poulenc Rorer concerning the forthcoming licence for Clexane in angina and MI in April. The complainant having read the letter wanted to examine the detail of the ESSENCE study and telephoned Rhône-Poulenc Rorer to request a copy. The complainant was informed that the study was not available for general release but a congress report that briefly summarised the ESSENCE study would be sent.

The complainant duly received the congress report and again telephoned the company to speak to one of the authors of the original letter. The complainant's request for a copy of the ESSENCE study was refused, the explanation being that it had not yet been published.

The complainant alleged a breach of Clause 7.4 of the Code as the company had not provided a copy of the ESSENCE study.

The complainant wrote a second letter to the Authority

stating that on 9 June 1997 he had received a more extensive abstract of the ESSENCE study from Rhône-Poulenc Rorer. This had been sent in response to his second request in April for a copy of the study. The complainant still considered that this was unsatisfactory.

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In writing to Rhône-Poulenc Rorer, the Authority stated that its view was that the general requirements of the Code such as Clause 7 would apply to materials supplied as advance notification prior to receiving a licence for a product or an indication.

RESPONSE

Rhône-Poulenc Rorer stated that the letter was sent to clinical and medical directors of cardiology and accident and emergency units and purchasing pharmacists in anticipation of authorisation of a new indication for enoxaparin. The information was for financial planning purposes and did not constitute promotion of the product.

The complaint related to the request for a copy of the ESSENCE study. In response to the request, Rhône-Poulenc Rorer immediately sent a copy of the congress report which set out the relevant conclusions from the ESSENCE study. Publication of the study in full was expected in July or August and the company would be happy to supply a copy of the full publication at that time. The company submitted that it was not obliged by anything in the letter or the spirit of the Code to supply copies of in-house reports where a synopsis covering the relevant details was available and provided. The company submitted that it acted promptly in providing the summary referred to and it had fulfilled its obligations under the Code.

PANEL RULING

The Panel noted that supplementary information to Clause 3.1 dealt with the provision of advance notification of new products or product changes. This guidance had been supplemented following consideration of two cases relating to the provision of advance notification. Further guidance had been included in the Code of Practice Review, May 1996.

In the Panel's view the general principles of the Code would apply to information issued as advance notification.

The Panel made no comment about either the appropriateness of issuing the information or the intended audience, as there was no complaint about these aspects. The complaint referred solely to the failure to provide a copy of the ESSENCE study.

The Panel noted that under Clause 7.4 of the Code companies were required to provide substantiation for any information, claim or comparison without delay at the request of members of the health professions or appropriate administrative staff.

The Panel noted that the complainant had requested a copy of the ESSENCE study in April and had been provided with a congress report that summarised the study. The congress report appeared in a publication dated December 1996 and reported on the 69th scientific sessions of the American Heart Association meeting held in New Orleans in November 1996. On 5 June 1997, following the complaint to the Authority, Rhône-Poulenc Rorer wrote to the complainant to provide a copy of the study abstract which consisted of four pages. The company apologised for the delay but explained that it had taken longer than anticipated to prepare the summary as it had been prepared from a large report. The complainant was also sent an abstract from the British Cardiac Society Meeting which had been held in May and an article from a journal "Circulation".

The Panel noted that although the complainant had not been provided with the study report, he had been sent relevant data both in the congress report and in the study abstract. In the Panel's view the information provided was sufficient to meet the requirement that substantiation be provided upon request. The Panel therefore ruled no breach of Clause 7.4 of the Code.

Following its consideration of this case, the Panel noted that the letter included a reference to the currently licensed indication for Clexane. This meant that prescribing information as set out in Clause 4.2 of the Code should have been provided. The Panel requested that this be drawn to the attention of Rhône-Poulenc Rorer.

Complaint received **4 June 1997**

Case completed **24 July 1997**

CASE AUTH/567/6/97

PARKE-DAVIS v BAYER

Promotion of Lipobay

Parke-Davis complained about the promotion of Lipobay (cerivastatin) by Bayer. A press release, an article in MIMS and a detail aid were the items at issue.

It was alleged that the press release repeatedly described the potency of Lipobay without any mention of why this was relevant to clinical practice, if at all. The Panel noted that a number of claims directly or indirectly referred to potency. In the Panel's view, the frequent use and content of the claims, such as "This dosage is 50 to 100 times less than the dosage of other statins" implied that there was a clinical benefit in relation to the potency of cerivastatin when there was no evidence that this was so. The Panel considered that the press release was misleading and ruled it in breach.

Parke-Davis said that the press release described cerivastatin as having a greater effect than other statins in that it was in the efficacy range of the more potent statins, simvastatin and atorvastatin, but alleged that this was not so. The Panel noted that the press release did not claim that cerivastatin had a "greater effect" but the MIMS article did. The Panel considered that the statement in relation to the efficacy range of cerivastatin in the press release was not sufficiently qualified in relation to the clinical benefits and it was misleading to claim that Lipobay was in the efficacy range of atorvastatin and simvastatin as the evidence was inadequate. A breach of the Code was ruled. A breach was also ruled in relation to the MIMS article as Bayer had been shown it in draft but did not seem to have attempted to have it changed.

Parke-Davis also alleged that the cost comparison in the detail aid compared prices without taking account of efficacy therefore misleading by omission. The Panel accepted that the comparison was a mere comparison of the price of each therapy. There had been no comparison of efficacy either expressly or by implication. No breach was ruled.

Parke Davis & Co Limited made a number of allegations in relation to the promotion of Lipobay (cerivastatin) by Bayer plc Pharmaceutical Division. The material at issue was a press release dated 4 April 1997 consisting of three parts; the first document was headed "Lipobay: Product Profile", the second "Lipobay brings low dose option for patients with high cholesterol" and the third "Heart disease: The role of the statins". An article about Lipobay in MIMS, May 1997, and a detail aid (ref: 9LIP0010) were also the subject of complaint.

1 Press release and MIMS article - potency of cerivastatin

COMPLAINT

Parke-Davis alleged that the press release repeatedly described the potency of Lipobay without any mention of why this was relevant to clinical practice, if at all. The lipid lowering effect achieved with cerivastatin across its dosage range of 100 - 300 microgram (LDL-cholesterol was reduced by 21.5 - 31.3%) was not similar to all statins as stated in the press release, since Parke-Davis' product atorvastatin lowered LDL-cholesterol by 41 - 61% across its dosage range of 10 - 80mg daily. Such potency claims were to quote the Code "meaningless and irrelevant". It was a breach of the Code to use the potency of a product for promotional purposes unless a link to some specific clinical benefit was described. Parke-Davis alleged that the press release and the MIMS article were in breach of Clauses 7.1 and 7.2 of the Code.

RESPONSE

Press release

Bayer submitted that the press release did not make repeated references to the potency of cerivastatin as alleged. The press release included information on the molecule which was of a purely scientific and general informational nature and was not in any way promotional. No repeated references to potency were included. The sole use of this word was in a quotation in the Trials Update section by Dr Evan Stein from the Metabolic and Atherosclerosis Research Centre, Cincinnati, USA. This was clearly marked as a quote and was the expressed opinion of this world leading opinion leader in lipidology. The company stated that it took very great care to ensure that this quote was not associated with the efficacy section for cerivastatin, as there was no evidence that the potency of a statin had any relevance to clinical efficacy.

Bayer submitted that potency *per se* was an issue which was raised by the Medicines Control Agency (MCA) in the labelling of the packaging for Lipobay. Bayer was asked to state in full the dosage of the product in *micrograms* on the pack (cf mcg), because the MCA was concerned that doctors and pharmacists should be made aware that Lipobay was not a milligram dosage as for the other statins. Bayer stated that it should, as a company, reinforce this to doctors and pharmacists together with the reasons why cerivastatin was a microgram dosage, in order to prevent confusion and the potential for inaccurate dosing. At no point in the promotional materials had the relative potency of cerivastatin been associated with its efficacy, as this would be quite wrong.

With regard to the relevance to clinical practice of lowering LDL-cholesterol by 21.5 - 31.3% with Lipobay compared with the 41 - 61% reduction claimed for Lipitor, Bayer submitted that the 4S, CARE and WOSCOPS trials showed clinical benefits (in terms of 'hard endpoint' reductions in morbidity and mortality) associated with 26 - 35% reductions in cholesterol. No evidence was available to show whether the 41 - 61% reductions in cholesterol (a 'surrogate endpoint') claimed by Parke-Davis for Lipitor produced any greater benefit than the 26 - 35% reductions already demonstrated by CARE, 4S and WOSCOPS. Conversely, there was no evidence to show that a 20% reduction in cholesterol had any less effect on 'hard endpoint' clinical benefit.

Furthermore, the range of LDL-cholesterol lowering for Lipobay had been based on pooled efficacy data from 7 clinical trials involving 3267 patients valid for efficacy. In contrast, Parke-Davis had selectively used data from only two studies: Black 1994 who looked at 350 patients with a dosage range of 2.5 - 80mg atorvastatin; and Nawrocki 1995 who looked at only 81 patients with the same dosage range. Bayer was aware of four further studies which would suggest that the range of LDL-cholesterol lowering with atorvastatin across its licensed dosage range varied from those claimed by Parke-Davis. These were:

Davidson 1997; which showed a reduction in LDL-cholesterol of 37% after 52 weeks' treatment with 10mg atorvastatin.

Bakker-Arkema 1996; which showed a reduction in LDL-cholesterol of 33.2% with 20mg atorvastatin and 41.4% with 80mg atorvastatin after 4 weeks of treatment.

Bertolini 1997; which showed a reduction in LDL-cholesterol of 35% after 52 weeks' treatment with 10mg or 20mg atorvastatin.

Nakamura 1997; which showed a reduction in LDL-cholesterol of 38% with 10mg atorvastatin and 50% with 20mg atorvastatin after 8 weeks' treatment.

Bayer submitted that clearly there were variations in the reduction of this surrogate marker which had not been taken into account by Parke-Davis.

MIMS article

Bayer said that MIMS (Monthly Index of Medical Specialities), in common with other publications, was informed by Bayer's public relations consultant of the launch of Lipobay. MIMS then, as was usual, made a request by telephone for scientific and clinical information on the product together with a press release. In this respect the information sent to MIMS was in response to a specific request for information. The summary of product characteristics (SPC), data on file, published papers and press release sent to MIMS were provided by Bayer together with a letter dated 18 June from the public relations consultant sent to Bayer. From this it was quite clear that the information supplied to MIMS was of a purely scientific and general informational nature and that although Bayer was asked for comment on the draft, full editorial control was retained by MIMS. Indeed the only comments made on the draft by Bayer were to ensure consistency with the SPC, without influencing editorial opinion.

The company submitted that it had acted in a professional and ethical manner and it was not in breach of the Code of Practice Clauses 7.1 and 7.2.

PANEL RULING

The Panel examined the press release and noted that the document headed "Lipobay: Product profile" included claims such as "Low dose, once daily treatment", "This dosage is 50 to 100 times less than the dosage of other statins" and "The LDL-cholesterol reductions of 30% produced by only 200mcg daily in this study clearly indicate that this agent is in the efficacy range of the more potent statins, simvastatin and atorvastatin. In fact, in terms of relative potency, cerivastatin is the most potent statin described in humans to date, at 25 times the potency of the next most potent statin".

The document headed "Lipobay brings low dose option for patients with high cholesterol" included the claims "Lipobay - a low dose, once daily treatment...", "Other statins require doses 50 - 100 times greater to achieve similar changes" and "The substantially lower doses needed to achieve the same cholesterol reduction as moderate or high doses of other statins, as well as the lack of significant side effects in clinical trials, offer physicians an exciting new alternative for achieving target cholesterol levels".

The Panel noted that each of the above claims directly or indirectly referred to potency. It was irrelevant that quotations from experts in the area had been used as it was an established principle under the Code that companies were responsible for everything in their material as if they had written it themselves. In the Panel's view, the frequent use and the content of the claims implied that there was a clinical benefit in relation to the potency of cerivastatin when there was no evidence that this was so. The Panel ruled that the two parts of the press release referred to above were misleading in this regard in breach of Clause 7.2 of the Code.

The Panel noted that in general companies were not responsible for the content of articles published in journals etc. Complaints about such matters were judged on the information provided by the company to the journalist/publication etc. Bayer had notified MIMS of the launch of Lipobay and MIMS had asked for further information. The Panel noted that Bayer had been asked to comment on the MIMS article. The Panel considered, in the circumstances, that it was not necessary to make a separate ruling regarding the MIMS article as it had already ruled that two parts of the press release were in breach of the Code.

The Panel did not accept that there was a breach of Clause 7.1 of the Code and ruled accordingly.

2 Press release and MIMS article - efficacy of cerivastatin

COMPLAINT

Parke-Davis stated that the press release described a "greater effect" than other statins and also stated that "this agent is in the efficacy range of the more potent statins simvastatin and atorvastatin". Parke-Davis' view was that firstly, cerivastatin did not have a greater effect than either agent and secondly, the effect cerivastatin had was not comparable to either simvastatin or atorvastatin. The MIMS article similarly described a "greater effect" than other statins.

Parke-Davis stated that the effect of cerivastatin was no greater, and was, in fact, considerably less than that of atorvastatin which lowered LDL-cholesterol by 41 - 61% across its dosage range of 10 - 80mg daily. Clearly, atorvastatin at 10mg daily lowered LDL-cholesterol more than that reported with the maximum licensed dose of 300 microgram daily with cerivastatin. Providing information to MIMS, or any other such publication, for the purposes of gaining editorial comment, represented a promotional activity and was therefore subject to the Code. It was the

responsibility of Bayer in reviewing copy for any such article to ensure that it was factually and technically correct, and reflected all of the available data.

The potency of cerivastatin was completely irrelevant to any discussion regarding efficacy. Bayer was clearly promoting on a platform which confused potency and efficacy, which Parke-Davis alleged misled physicians. The marketing department reported that doctors were indeed being confused and therefore misled with regard to potency, cost, and efficacy.

RESPONSE

Press release

Bayer submitted that at no point in the press release was it stated that cerivastatin had a "greater effect" than other statins. It was therefore not able to comment on this particular point. As described under the previous point there was no evidence that lowering cholesterol by the 41 - 61% claimed for Lipitor had any greater clinical benefit in reduction of morbidity and mortality than lowering cholesterol by the 21.5 - 31.3% demonstrated for Lipobay.

The quote in the press release: "this agent is in the efficacy range of the more potent statins simvastatin and atorvastatin" was a direct quote from Stein 1997. It was clearly indicated as such, and represented the current opinion of this leading lipidologist. His views were similarly echoed by the current literature, Insull 1997; Angerbauer 1994; Bischoff 1997; Corsini 1996. It was also clear that as cerivastatin was a new compound and as publications were appearing in scientific journals, this issue was one of emerging scientific and clinical opinion which had not been resolved in favour of any one opinion.

Bayer pointed out that in the 4S secondary prevention study, a reduction in the surrogate marker LDL-cholesterol of 35% with 20 or 40mg of simvastatin was achieved. Cerivastatin reduced LDL-cholesterol by up to 31.3% in the pooled efficacy analysis enclosed with the response. Clearly in terms of reduction of LDL-cholesterol alone, cerivastatin produced the same order of reduction as simvastatin.

Bayer pointed out that the quote came under the heading "Trials Update" and did not appear under the clinical section of the piece. Bayer submitted that it had clearly differentiated any discussion on the potency of the statins from the efficacy of cerivastatin in the press release and all the promotional literature. In addition, at no point in the press release were any statements made regarding the efficacy of cerivastatin which were not backed up by data from clinical trials. Bayer submitted that it could not be held responsible for journalists who took quotes out of context but it was incumbent on Bayer, as a leading pharmaceutical company, to provide as much information regarding its product as deemed to be appropriate. All the promotional materials for medical professionals clearly stated the efficacy ranges for cerivastatin. It was the prescriber's responsibility to interpret this information and act accordingly to choose the appropriate dose for individual patients.

MIMS article

With regard to Parke-Davis' allegation that providing information to MIMS was subject to the ABPI Code, Bayer drew attention to Clause 1.2 that "factual, accurate, informative announcements and reference material relating, for example, to pack changes, adverse-reaction warnings, trade catalogues and price lists, provided they include no product claims" were not subject to the Code. Furthermore the information provided to MIMS was, as already explained, given in response to a specific request for information. Apart from the purely scientific information provided (SPC, published papers, and data on file), MIMS specifically requested a copy of the press release. It was not incumbent on Bayer to provide MIMS with information pertinent to other companies' products. The article in MIMS was written entirely by MIMS which had complete editorial control, as explained under point 1 above. Therefore it was not possible for Bayer to have breached Clause 7.2 of the Code as alleged.

PANEL RULING

The Panel noted that Clause 1.2 of the Code exempted from the definition of promotion factual, accurate, informative announcements and reference material relating, for example, to pack changes, adverse-reaction warnings, trade catalogues and price lists, provided they included no product claims. In the Panel's view the exemption did not apply to the press release as it included product claims. Neither did the exemption relating to replies to individual enquiries apply as Bayer had informed MIMS of the launch of Lipobay. The exemption related to unsolicited requests for information and not solicited requests as had happened in this instance.

The Panel noted that the part of the press release headed "Lipobay: Product profile" stated "The authors concluded: 'The LDL-cholesterol reductions of 30% produced by only 200mcg daily in this study clearly indicate that this agent is in the efficacy range of the more potent statins, simvastatin and atorvastatin. In fact, in terms of relative potency, cerivastatin is the most potent statin described in humans to date, at 25 times the potency of the next most potent statin.' " The press release did not claim that cerivastatin had a "greater effect" as alleged.

The Panel noted that Lipobay lowered cholesterol by 21.5 - 31.3%. A reduction of 41 - 61% was claimed for atorvastatin across its dosage range of 10 - 80mg daily. Bayer quoted four papers with values below this range. The lowest being 33.2% with 20mg in patients with hypertriglyceridaemia. Other values with 10mg in hypercholesterolaemia were 35, 37 and 38%.

The Panel accepted that the data suggested that the higher doses of Lipobay might reduce cholesterol to a similar extent as the lower doses of atorvastatin given the data submitted by Bayer. Only to this extent might Lipobay be described as being "in the efficacy range of ...atorvastatin". The Panel noted the submission from Bayer that there was no evidence that lowering cholesterol by 41 - 61% as claimed for atorvastatin had any greater clinical benefit in reduction of morbidity and mortality than lowering of cholesterol by the 21.5 - 31.3% demonstrated for Lipobay. The Panel noted Bayer's submission that in the 4S study a reduction in the surrogate marker LDL-cholesterol of 35% with 20 or 40mg of simvastatin was achieved.

The Panel decided that the statement relating to the efficacy range of cerivastatin in the press release was not

sufficiently qualified in relation to the clinical benefits. Further, in the Panel's view it was misleading to claim that Lipobay was in the efficacy range of atorvastatin and simvastatin as the evidence was inadequate. The Panel therefore ruled that the press release was misleading in breach of Clause 7.2 of the Code.

With regard to the article in MIMS, the Panel noted that it stated "In comparison with other statins, cerivastatin is considered to be a highly potent agent. Other compounds require doses 50 to 100 times greater to achieve a similar reduction in LDL-cholesterol". Despite the greater effect, there was no evidence of increased risk of side-effects with cerivastatin. The Panel noted that the article implied that there was a benefit in the greater potency and there was no data to substantiate the claim for a greater effect.

The Panel noted that unlike point 1 above, there was a difference between the content of the press release and the MIMS article. The press release did not claim that cerivastatin had a "greater effect" but the article in MIMS did. The Panel noted that Bayer had seen the MIMS article and had been able to comment upon it but full editorial control was retained by MIMS. The Panel had no evidence as to whether Bayer had attempted to correct the article in MIMS. The Panel accepted that comments made by the company might be ignored but considered that the company's failure to attempt to correct the article in relation to the reference to "greater effect" meant that the company was responsible for the content which was misleading. The Panel therefore ruled a breach of Clause 7.2 of the Code.

3 Detail aid - cost comparison

The page at issue was headed "Lipobay - a rationally priced therapy" and gave a comparison chart of the cost of 28 days' treatment and recommended minimum to maximum daily dosage for Lipobay, fluvastatin, simvastatin, pravastatin and atorvastatin. The price of Lipobay was between £12.95 and £18.20 whereas the price of atorvastatin was £18.88 to £94.08. The dosage range for each product was also given.

COMPLAINT

Parke-Davis alleged that in this therapeutic area it was wholly inappropriate to describe cost alone in the manner Bayer had chosen. The full range of doses for each product was described but the comparison was misleading since it excluded evidence of efficacy. The supplementary information to Clause 7.2 of the Code stated that "Price comparisons, as with any other comparison, must be accurate, fair and must not mislead. Valid comparisons can only be made where like is compared with like." The data available showed very clearly that the lipid lowering effect of atorvastatin was very different to that of cerivastatin - atorvastatin 10mg daily lowered LDL-cholesterol by 41% whereas cerivastatin 300 microgram only lowered LDL-cholesterol by 31.2%. Such a comparison should not mislead, either directly or by implication. This comparison included the full range of doses for each product but no information whatsoever in respect of efficacy and was therefore incomplete and misleading by omission. Furthermore, the range of indications for all of the products cited was different. Breaches of Clauses 7.2 and 7.6 of the Code were alleged.

RESPONSE

Bayer submitted that the argument by Parke-Davis that cost must be linked with efficacy was spurious. In no other area of medicine did this occur. It was simply not possible to compare the efficacy of two completely different compounds, with different pharmacological profiles, and relate this to cost.

The price comparison chart simply showed the prices of each of the statins on a zeroed scale which was entirely accurate. It was not misleading as like was entirely compared with like i.e. cost across the dosage range of all available products. No attempt had been made to link efficacy to cost. The appropriate dose of a statin could only be determined by the prescriber in relation to individual patient requirements. The doctor must balance the needs of the patient with all available treatments together with their pharmacological and therapeutic profiles, including efficacy, safety and drug interactions. It might not be appropriate for example for a patient to be exposed to the higher reductions in LDL-cholesterol and triglycerides associated with the recommended 10mg starting dosage of atorvastatin, as compared with the reductions achieved with the 100 microgram starting dosage of cerivastatin. Moreover, the drug interaction profiles of the two compounds also differed. Indeed this was particularly important in the light of a recent warning from the Medical Defence Union to its member doctors concerning drug interactions with warfarin.

As outlined under the previous points, there was no evidence whatsoever that the reductions in cholesterol of 41 - 61% claimed for Lipitor had any increased clinical benefit over the 21.5 - 31.3% reductions determined for Lipobay across its licensed dosage range. Bayer quoted a reference by Jackson 1997; in which this very issue was raised: "It is vitally important to remember that the clinical not the biochemical benefit is our endpoint and we must not be seduced by bigger and better biochemical results if they have no clinical meaning. A sledgehammer is rarely needed to crack a nut". This illustrated that the issue was one of an emerging scientific and clinical opinion as referred to in Clause 7.2 of the Code.

PANEL RULING

The Panel noted that the promotional material provided by the complainant (ref 9LIPO010) was slightly different to the promotional material provided by the respondent (ref 9LIPO009) in that the detail aid (ref 9LIPO010) included the claim "A rationally priced therapy" and the detail aid (ref 9LIPO009) included the claim "Rationally priced". The Panel made its ruling on the detail aid provided by the complainant (ref 9LIPO010) though the issue involved seemed to be common to both items.

The Panel did not agree with Bayer's view that it was not possible to compare the efficacy of two completely different compounds and relate this to cost. In the Panel's view this was the principal objective of pharmacoeconomic evaluation studies.

The Panel noted that it appeared to be acknowledged by both parties that there were differences in the extent of cholesterol lowering as between the statins and there was

data to support the greater cholesterol lowering of atorvastatin compared to Lipobay. The Panel noted Bayer's view that the 4S, CARE and WOSCOPS trials showed clinical benefit (in terms of hard endpoint reductions in morbidity and mortality) associated with 26 - 35% reductions in cholesterol. No evidence was available to show whether the 41 - 61% reductions in cholesterol (a surrogate endpoint) claimed by Parke-Davis for Lipitor produced any greater benefit than the 26 - 35% reductions demonstrated by 4S, CARE and WOSCOPS. Conversely there was no evidence to show that a 20% reduction in cholesterol had any less effect on 'hard endpoint' clinical benefit.

Noting the above points, the Panel nonetheless considered that the cost comparison was a mere comparison of the price of each statin therapy. There was no comparison of efficacy though the meaning intended to be attached to the expression "rationally priced" was somewhat opaque - presumably most pricing decisions had at least an element of rationality about them. It was generally accepted that price comparisons could be made based on cost only without considerations of the relative efficacies of the products compared provided that the question of relative efficacy was not featured in the comparison either expressly or by implication. The Panel therefore ruled no breach of the Code.

Complaint received **13 June 1997**

Case completed **3 September 1997**

CASE AUTH/568/6/97

JANSSEN-CILAG v LUNDBECK

Echo Programme

Janssen-Cilag alleged that a booklet issued by Lundbeck which described its Echo Programme, an ECG monitoring service for psychiatrists and their patients, was aimed at facilitating the use of sertindole (Lundbeck's product Serdolect). It was thus a promotional item but it lacked prescribing information. Janssen-Cilag objected to the inference that its product Risperdal (risperidone) had the same cardiac toxicity as sertindole. The Echo Programme itself was alleged to be disguised promotion in breach of the Code.

The Panel noted that the Echo Programme was open to patients prescribed antipsychotic medicines and was not restricted to patients prescribed Lundbeck's product. The service would benefit patient care. The Panel did not accept that it constituted disguised promotion of sertindole and no breach was ruled in that regard.

The Panel considered that a table in the booklet was misleading and unfair in that the impression given was that there would be similar concerns with Risperdal to those with sertindole regarding lengthening of QT intervals, but there was no evidence that this was so. The table and other references in the booklet to problems with cardiac toxicity of antipsychotics were disparaging of Risperdal and ruled in breach.

In the Panel's view, the inclusion of the table meant that prescribing information was needed and as it was not present a breach of the Code was ruled. The Echo Programme had to be non-promotional in order to comply with Clause 18 of the Code and the brochure accordingly needed to be amended to make it non-promotional in nature.

Janssen-Cilag Ltd complained about the Echo Programme which was part of the Lundbeck Schizophrenia Disease Management Programme. Lundbeck Limited, although not a member of the ABPI, had nevertheless agreed to comply with the Code.

Details of the Echo Programme appeared in a booklet "Making ECG a routine part of patients' care". The booklet described the programme which was an ECG monitoring service for psychiatrists and their patients. The booklet referred to the mortality of psychiatric patients and to the benefits of baseline and regular ECG screening.

COMPLAINT

Janssen-Cilag said that sertindole (Serdolect), Lundbeck's product for schizophrenia, was launched in 1996. At that time the summary of product characteristics (SPC) carried a warning regarding QT interval prolongation and stated that an ECG should be performed before initiation. This did not appear to deter initial use of the product. However, Janssen-Cilag said that following reports of a number of deaths amongst patients receiving sertindole, the SPC recommendation was reinforced and now included a requirement for regular ECG monitoring whilst on therapy. Janssen-Cilag's view was that this presented a more significant barrier to prescription and consequently a serious set-back for the marketing of the product. The Echo Programme was apparently part of a schizophrenia disease management programme and concerned the routine use of ECGs for patients receiving antipsychotic medication and the offer of a service facilitating this procedure.

Janssen-Cilag said that the booklet mentioned sertindole along with several competitor antipsychotics in a comparative table. It made claims about Lundbeck's standing in the field of psychiatry. It was manifestly aimed at facilitating the use of sertindole by helping overcome the requirement for an initial and subsequent ECGs. Sertindole was the only major product that had this requirement. Janssen-Cilag therefore alleged that the booklet was a promotional item lacking prescribing information in breach of Clause 4.1 and that the programme itself constituted a disguised promotional activity in breach of Clause 10.1 of the Code.

Janssen-Cilag said that the booklet was unduly alarmist

and inherently questioned the safety of all antipsychotic medication in the UK. Page 1 entitled "Mortality and psychiatric patients a cause for concern" inferred that all antipsychotic medications carried a significant additional risk of death in the psychiatric population through cardiac abnormalities. Janssen-Cilag objected most strongly to the inference that its product Risperdal (risperidone) had the same cardiac toxicity as sertindole. A breach of Clause 8.1 of the Code was alleged.

Janssen-Cilag said the justification for the inclusion of risperidone in the table on page 2 headed "Overview of cardiovascular events with antipsychotics" was a small section in the US data sheet which was not present in the UK SPC. Risperidone was included under a heading of "QT interval" without any clarification or commentary with the apparent intention of inferring equality to sertindole with regard to cardiac safety. This was not borne out in any trial work or clinical practice and was a misleading representation of the facts. The presentation of risperidone in the table was alleged to be in breach of Clause 7.2 of the Code.

Janssen-Cilag was concerned that the booklet appeared to be intended to undermine physician confidence in antipsychotic medication for the sole purpose of overcoming a marketing issue relating to the requirement for ECG monitoring prior to and during prescription of sertindole. Janssen-Cilag sought advice as to whether the use of a safety monitoring requirement for promotional purposes was something that should be severely discouraged.

RESPONSE

Lundbeck said that sertindole was launched in the UK in June 1996 with a SPC approved by the Medicines Control Agency. Effects upon cardiac repolarisation were identified in early development and consequently mild prolongation of the QT interval was identified in some patients. For this reason the SPC mandated a baseline ECG before starting treatment. Licences throughout Europe were sought using the mutual recognition procedure. The requirement for ECG monitoring on the resultant European SPC was a result of this process and not a consequence of reported deaths associated with sertindole.

Lundbeck stated that the Echo Programme was developed as a non-promotional service to help psychiatrists perform ECGs on their patients receiving antipsychotic medication. Cardiac conduction problems were known to be associated with most antipsychotics and could have very serious consequences. This was becoming recognised more widely with, for example, the publication of guidelines for ECG monitoring of patients receiving high dose antipsychotics from the Royal College of Psychiatrists. Lundbeck submitted that addressing this issue was not unduly alarming but necessary and responsible. Discussions with many psychiatrists had revealed both a desire to increase ECG recording and practical difficulties in doing so. Having identified an area of unmet need, Lundbeck saw the utility of an ECG service. The service was not linked to use of sertindole in any way and psychiatrists were free to perform ECGs on any patient receiving antipsychotic medication. Sertindole was mentioned in the supporting booklet only once and was treated no differently from the other antipsychotics mentioned. The company did not suggest that ECG monitoring should always be carried out on patients receiving antipsychotics other than sertindole. A cardinal feature of the service was that the decision to perform an ECG was left entirely with the psychiatrist according to their clinical judgement. The company submitted that the frequent presence of cardiac risk factors in patients receiving antipsychotics (for example, hypertension, smoking and obesity) and overt cardiac disease made ECGs necessary in many cases. Such patients would receive ECGs as part of routine general medical care and the company submitted that psychiatric patients were entitled to the same standard of care. The need for ECGs to be considered as part of the routine management of schizophrenia extended beyond the cardiac risk profile of the specific medicine.

The company submitted that the Echo Programme was a legitimate disease management initiative and neither the programme nor the book was promotional.

In order to evaluate the feasibility of supporting such a service the booklet would initially be given to a limited number of psychiatrists who expressed an interest in the programme. The purpose of the booklet was to describe the ECG procedure and the logistics of obtaining an ECG report. Some background information was given in the first few pages which outlined the very important issue of cardiac conduction problems in patients with schizophrenia. The table on page 2 merely listed cardiac problems stated in the products' data sheets or SPCs. This source was clearly stated beneath the table and the identification of these facts in no way implied an assessment of differential associated risk. It was nowhere stated or implied that cardiac problems were associated with all antipsychotics. Risperidone was included because reference to QT interval prolongation was made in the US labelling. This was also stated clearly. The company submitted that US labelling was a legitimate source of safety information and inclusion of risperidone was not a breach of Clause 7.2. The table merely stated facts derived from regulatory documents and did not address associated risks. The company did not imply that risperidone and sertindole had the same potential for cardiac toxicity. It was important to stress that QT interval prolongation associated with sertindole had not been linked to outcomes suggesting manifest cardiac toxicity. Any risks associated with this phenomenon were largely theoretical and had not been demonstrated in clinical practice. The allegation of the breach of Clause 8.1 implied that sertindole was associated with significant cardiac toxicity. This was not supported by the facts and therefore the clause had not been breached.

The Echo Programme was not intended to undermine physician confidence in antipsychotic medication. On the contrary it was intended to improve confidence by providing psychiatrists with a means of assessing the cardiac status of their patients whenever they considered it was necessary. The programme supported psychiatrists in carrying out an important investigation which was often otherwise difficult to perform for logistical reasons.

PANEL RULING

The Panel noted that in the Echo programme booklet page

1 referred to deaths of psychiatric patients. It stated that in overdose striking cardiac abnormalities in function and rhythm occurred. Further that high doses of antipsychotic medicines might be associated with abnormally prolonged QT intervals and that a linear relationship between QT prolongation and propensity for malignant cardiac arrhythmia and sudden cardiac death had been established. According to the booklet virtually all antipsychotic medicines carried warnings in their SPCs cautioning over cardiac events.

The table on page 2 was headed "Overview of cardiovascular events with antipsychotics" and listed a number of products. The table indicated that "QT interval" was an event associated with risperidone and with sertindole. A reference "b" was given for risperidone which was explained underneath the table as being "According to the US data sheet". The information for the other products was attributed to information taken from UK manufacturers' data sheets. The following page was headed "ECG : good clinical practice" and mentioned that as antipsychotics were frequently prescribed in high doses and in combination, the potential for cardiac abnormalities meant that ECG screening was increasingly being viewed as good clinical practice. Reference was made to the Royal College of Psychiatrists' Consensus Statement on the use of high dose antipsychotic medication (1993) which recommended obtaining an ECG prior to initiating patients on high dose therapy and performing regular monitoring while such treatment continued. The booklet stated that the potential benefit of conducting ECGs in all patients was not insignificant.

The booklet gave reasons for the low uptake of ECG screening and then referred to the service in detail. The service provided an initial 150 free qualifying ECGs. To qualify each ECG had to be performed on a patient receiving antipsychotic medication. The booklet stated that in the first year availability of the Echo programme would be restricted to the first 300 psychiatrists and that Lundbeck reserved the right to restrict distribution of the Echo programme. The service was administered by Lundbeck representatives. The Panel did not have any documents relating to the instructions for representatives.

In the Panel's view the booklet was subject to the Code as it referred to an area in which the company had a commercial interest. Treatments were mentioned.

The Panel noted that the Echo programme was open to patients prescribed antipsychotic medication. It was not restricted to patients prescribed the Lundbeck product. Reporting and interpretation of data for non qualifying patients was at cost. The service would benefit patient care. The results of the ECG would be back within 30 minutes. The Panel did not accept that the Echo programme constituted disguised promotion of sertindole. No breach of Clause 10.1 of the Code ruled.

The Panel noted that the SPC for Risperdal stated that a prolonged QT interval was reported in a patient with concomitant hypokalaemia who had ingested 360mg. The patient had made an uneventful recovery. The SPC stated that the usual effective dosage was 4 to 8 mg/day and doses above 16 mg/day had not been extensively evaluated for safety and should not be used.

The Panel noted that the Physicians Desk Reference stated that risperidone and/or 9-hydroxyrisperidone "... appears to lengthen the QT interval in some patients, although there was no average increase in treated patients, even at 12-16 mg/day, well above the recommended dose." The Physicians Desk Reference stated that bradycardia, electrolyte imbalance, concomitant use with other drugs that prolonged QT or the presence of congenital prolongation in QT could increase the risk of occurrence of this arrhythmia.

The Panel noted that the SPC for Serdolect stated that the product lengthened the QT interval in some patients and that the risk of QT prolongation was increased in patients receiving concomitant treatment with medicines that prolonged the QT interval.

The Panel considered that the table was misleading and unfair in that the impression given was that there would be similar concerns with risperidone to those with sertindole regarding lengthening of the QT interval and there was no evidence that this was so. The Panel therefore ruled a breach of Clause 7.2 of the Code. The table and other references in the booklet to problems with cardiac toxicity with antipsychotics were disparaging of risperidone as alleged. A breach of Clause 8.1 of the Code was ruled.

The inclusion of the table meant that prescribing information was required. A breach of Clause 4.1 of the Code was ruled. The Panel noted that the Echo programme must not be promotional in order to be within the exemption to Clause 18.1 relating to the provision of medical and educational goods and services which would enhance patient care and benefit the NHS. The provision of such goods and services must not be done in such a way as to be an inducement to prescribe, supply, administer or buy any medicine. In order to comply with the Code the booklet needed to be amended so that it did not constitute promotional material with the consequent requirement that prescribing information be provided.

Complaint received **11 June 1997**

Case completed **1 August 1997**

CASE AUTH/569/6/97

BIOGEN v SCHERING HEALTH CARE

Betaferon press materials

Biogen complained about a press release issued by Schering Health Care which compared interferon-1a (Biogen's product Avonex) with interferon-1b (Schering Health Care's product Betaferon).

A statement in the press release compared the self administration by subcutaneous injection of Betaferon with the deep intramuscular injection of interferon-1a. The Panel considered that the press release gave the impression that, in the short term, Betaferon was better tolerated than Avonex and that, in the long run, there were safety considerations associated with Avonex. The Panel considered that such an impression was unbalanced, misleading and not capable of substantiation and ruled it in breach of the Code.

A statement that Biogen was currently conducting trials with the subcutaneous route was ruled to be in breach as it was inaccurate. Biogen was not investigating the possibility of a subcutaneous formulation of Avonex.

Also ruled in breach was a statement that more injection site reactions were seen with Betaferon than with interferon-1a but that it must be remembered that Betaferon injections were self-administered whereas interferon-1a was injected by healthcare professionals. The Panel considered that this was misleading with regard to the incidence and cause of injection site reactions.

A further statement alleged to be misleading said that questions had been posed with regard to the dose of interferon-1a, that many experts believed it was too low and that in the USA the FDA had asked for additional studies to be done with double and triple the dosage used in the pivotal trial. This statement was inaccurate. The FDA had not asked for additional studies to be done as stated. The Panel noted that the SPCs for both products indicated that their optimal doses had not been established. The Panel considered that giving this information for Avonex but not for Betaferon was misleading and ruled it in breach. The Panel considered that readers would assume by implication that the optimal dose of Betaferon had been established which was not so.

The statement that the Betaferon study was not designed to show a significant effect on progression of disability but that nonetheless a strong trend toward the slowing of disease progression was observed was ruled in breach. The Panel considered that it was misleading to claim in the press release that Betaferon had a beneficial effect on disease progression given the information in the SPC and the design of the trial.

A further breach was ruled in relation to a statement that the reduction in relapse rate was far greater with Betaferon than with interferon-1a and that this represented an increased likelihood of remaining relapse free at two years with Betaferon as compared with interferon-1a. According to the respective SPCs, the reductions in relapse rates were very similar and the Panel considered that the brevity of the statement gave a misleading impression of the reductions in relapse rates of the two products.

A statement relating to the deterioration of placebo patients more quickly than might have been expected from natural history studies of multiple sclerosis and that it was this level of deterioration that gave rise to the statistical significance of the study on interferon-1a was ruled to be in breach. The Panel noted that the press release effectively condemned a study for having the wrong type of patients in its placebo arm. The Panel considered that the evidence for this was equivocal and had only been raised as a theoretical possibility. The comments made about the study in the press release were considered by the Panel to be unbalanced and misleading.

The Panel considered that the critical references to Avonex were not accurate, balanced or fair and that the overall effect amounted to disparagement and a breach was ruled. The Panel also ruled a breach in relation to an allegation that the press release failed to maintain a high standard.

The Panel did not consider that the press release amounted to advertising to the general public as alleged and nor did it consider that the press release brought discredit upon and reduced confidence in the pharmaceutical industry.

Biogen Limited complained about a press release issued in March 1997 by Schering Health Care Limited. The press release compared Betaferon (interferon beta-1b) with interferon beta-1a (Avonex) in the treatment of multiple sclerosis. Avonex had just been launched by Biogen while Betaferon had been available from Schering Health Care since December 1995

1 **"Betaferon is self-administered by a simple subcutaneous injection ... 1a requires a deep intramuscular injection ... The intramuscular route requires deep injections with relatively large needles, and there are safety concerns when such injections are required on a chronic, long-term basis, as they are in patients with MS. The smaller needles used in subcutaneous injections ... represent less discomfort for patients, while self-injection generally gives them greater control and flexibility over their therapy."**

COMPLAINT

Biogen said that although Schering Health Care might contend that this statement merely suggested that long-term intramuscular (IM) injection of any medicinal product could be accompanied by safety concerns, Biogen believed that, taken in context, the statement was clearly intended to create the impression that long-term IM administration of Avonex might be unsafe. This suggestion was false and misleading, and it was likely to create unwarranted public anxiety about the safety of an approved medicine.

First, there was, quite simply, no evidence from clinical trials or clinical practice that there was a greater "safety concern" associated with long-term IM injection of Avonex under approved conditions of use versus long-term subcutaneous administration of Betaferon. The statement

was therefore unsubstantiated and false.

Biogen said that in addition the statement omitted the fact that the use of Betaferon under approved conditions was associated with a greater risk of injection site reactions than Avonex. This difference between the two products was made clear by the approved European Community labelling (summaries of product characteristics (SPCs) and package leaflets); the approved labelling in the United States; a formal determination by the United States Food and Drug Administration (FDA); and experience from clinical trials and post-marketing adverse reaction reports.

Biogen pointed out that the SPC for Betaferon stated that "Injection site reactions occurred frequently after administration ... inflammation, pain, hypersensitivity, necrosis and non-specific reactions were significantly associated ...". In contrast, the SPC for Avonex included injection site reactions among "Other less common adverse events". Substantially similar information appeared in the products' respective package leaflets.

Biogen said that under provisions of US medicines law applicable to "orphan drugs", the FDA was permitted to approve Avonex only after determining that it was "clinically superior" to interferon beta-1b. This determination was set out in the FDA's Summary Basis of Approval for Avonex:

"Under the regulations of the Orphan Drug Act, Biogen's Interferon beta-1a was determined to be a different product from Chiron's Interferon beta-1b, because of a difference in safety profile involving the occurrence of injection site skin necrosis with the Chiron product, but not the Biogen product. Analyses of the safety data submitted in the Biogen PLA showed that no injection site necrosis was reported in the 158 patients treated with Interferon beta-1a in the phase 3 study (0%). In contrast, the incidence of injection site necrosis reported in Chiron's PLA was 5% in the 124 patients treated with Interferon beta-1b in the phase 3 study. Further supportive evidence for a difference in skin necrosis incidence is suggested by the 85% incidence of injection site reactions in the Chiron Phase 3 study versus only 4% in the Biogen phase 3 trial."

Biogen submitted that Schering Health Care must have been aware of this determination, because its US affiliate (Berlex Laboratories) brought an unsuccessful action for judicial review in the US courts to challenge the FDA's approval of Avonex, in which the FDA's finding of "clinical superiority" was upheld. Furthermore, the currently approved US package insert for interferon beta-1b further confirmed the risk of injection site reactions associated with the product:

"Injection site necrosis was reported in 5% of patients in a controlled MS trial ... Other injection site reactions occurred in eighty-five percent of patients in the controlled MS trial, at one or more times during therapy."

Finally, Biogen stated that evidence from clinical trials and post-marketing safety reports confirmed that the incidence of injection site reactions was much lower for Avonex than for Betaferon. There had not been a single reported case of injection site necrosis associated with use of Avonex in actual clinical practice (over 25,000 patients). The incidence of other injection site reactions had been comparable to that which was observed in the clinical trials reviewed by the US FDA and the European Community authorities.

For the reasons above, Biogen said that the statement cited was unbalanced and unfair, did not reflect the available evidence on side effects, and was misleading. It was likely to bring discredit upon or reduce public confidence in the pharmaceutical industry. Finally, by suggesting that Avonex was associated with safety risks that were not presented by Betaferon, it was made for the purpose of encouraging members of the public to ask their doctors to prescribe a particular medicine. Biogen alleged breaches of Clauses 2, 7.2, 7.3, 7.7, and 20.2.

RESPONSE

Schering Health Care contended that the press release did not claim or imply that long term administration of Avonex was unsafe, nor that the subcutaneous route of injection was risk-free, merely that this route was less painful and allowed easier self-administration. It was generally acknowledged that administering products subcutaneously provided a considerable increase in the number of potential injection sites, and minimal problems as shown by the experience with diabetic patients. Even in the absence of evidence of harm, it was undeniable that long-term intramuscular injections gave rise to safety concerns, and the relatively short experience with Avonex did not allay such concerns. As the statement related to the depth of injection, rather than the effects of the products on surrounding tissues, Schering Health Care considered that Biogen's reference to skin necrosis was irrelevant, and the company did not, therefore, believe that it was necessary to respond in detail to the various issues on this matter raised by Biogen. Schering Health Care said that omission of reference to injection site reactions was not misleading, as asserted by Biogen.

PANEL RULING

The Panel noted that the statement "The intramuscular route requires deep injections with relatively large needles, and there are safety concerns when such injections are required on a chronic long-term basis, ..." was a general statement. The addition of ".... as they are in patients with MS" however turned it into a more specific statement and, in the context of a press release which gave details of interferon-1a, inevitably linked it to that product in particular. The Panel considered that the majority of readers would assume that there were problems associated with the long-term use of Avonex by virtue of its route of administration. The Panel noted that this had not been shown.

The Panel considered that the statement "The smaller needles used in subcutaneous injections ... represent less discomfort for patients ..." gave the impression that, compared to IM injections of Avonex, the administration of the subcutaneous injections of Betaferon were less painful. The Panel noted, however, that the SPC for Betaferon stated that injection site reactions occurred frequently and included redness, swelling, discoloration, inflammation, pain, hypersensitivity and necrosis. The incidence of these reactions usually decreased over time. Conversely the SPC for Avonex listed "injection site reaction" (not specified) as a less common adverse event.

The Panel considered that the press release gave the impression that, in the short term, Betaferon was better tolerated than Avonex and that, in the long-term, there

were safety-concerns associated with the administration of Avonex. The Panel considered that such an impression was unbalanced and misleading. A breach of Clause 7.2 was ruled. The Panel also ruled a breach of Clause 7.3 as the statement was not capable of substantiation.

The Panel noted that the press release had gone almost exclusively to the medical / pharmaceutical press. Three lay publications, The Times, The Sunday Times and the Financial Times had received the press release. It had also been sent to a number of freelance journalists.

The Panel noted that the press release was very detailed and gave technical information about the products. The Panel considered that given its content and as it had been sent predominantly to the medical/pharmaceutical press it was more appropriate to consider the allegations in relation to Clause 7 and not to make any rulings regarding Clause 20.2.

The Panel considered that given its ruling of breaches of Clauses 7.2 and 7.3 it was not necessary to make any ruling regarding the alleged breach of Clause 7.7.

The Panel did not accept that the statement was in breach of Clause 2 of the Code and no breach of that Clause was ruled.

2 "Biogen, the manufacturers of 1a, are currently conducting trials with the subcutaneous route, suggesting that they too may be unsure about the appropriateness of intramuscular injections."

COMPLAINT

Biogen said that this statement was false. The company was not conducting at the time of the press releases, and was not currently conducting, any clinical studies involving subcutaneous injection of Avonex. The statement called into question the "appropriateness" of IM injections, which did not accurately reflect available evidence and suggested a lack of safety. Avonex was demonstrated to be effective in relapsing multiple sclerosis using IM injection and was approved in the EU for administration via that route, as stated in its SPC. Biogen alleged breaches of Clauses 7.2, 7.3, 7.7, and 20.2.

RESPONSE

Schering Health Care submitted that it had understood from external sources that studies were being carried out on behalf of Biogen with a subcutaneous route.

PANEL RULING

The Panel noted that the statement was inaccurate. Biogen was not investigating the possibility of a subcutaneous formulation of Avonex. A breach of Clause 7.2 was ruled. It was not necessary to make any further ruling regarding the alleged breaches of Clauses 7.3 and 7.7.

3 "More injection-site reactions were seen with Betaferon than with 1a but it must be remembered that the Betaferon injections were self-administered whereas 1a was injected by healthcare professionals."

COMPLAINT

Biogen stated that this statement suggested that more injection site reactions were found with 1b because of self-administration rather than the medicine itself, and that the more favourable results for Avonex were due to the provision of injections by healthcare professionals. By focusing on who administered the injection, this statement suggested that self-injection was less safe and downplayed a potential health hazard connected with 1b.

Biogen stated that Avonex was administered by healthcare professionals in the Phase 3 trial; however, many of these same trial patients were currently being followed in an ongoing study involving 382 patients. In this study, 5-10% of injections were being given by healthcare professionals, and 90-95% of injections were being administered at home. The rate of injection site reactions remained similar to those in the Phase 3 trial: 2% of patients had injection site reactions and no cases of skin necrosis had been reported.

With regard to the downplay of health hazards related to Schering Health Care's product, Biogen referred to point 1 above concerning the incidence of necrosis and other injection site reactions for 1b. This aspect was particularly worrisome as presented to the general public.

Biogen alleged breaches of Clause 7.2, 7.3, 7.7, and 20.2.

RESPONSE

Schering Health Care submitted that the statement did not suggest that self-injection was less safe than injection by healthcare professionals and did not downplay a potential health hazard connected with Betaferon, as asserted by Biogen. The sources of its information were the published trials of both 1a and 1b. The company had previously asked Biogen's solicitors for details of the unpublished data from the incomplete study to which reference was made in Biogen's complaint but these had not been forthcoming. The published data showed a clear difference between the method of administration of the injections of the two products and it was a reasonable inference to draw that this difference might have an effect on the number of injection site reactions in the respective studies. As Biogen deemed that patients on Avonex might safely self-administer the product, Schering Health Care submitted it was reasonable to point out that the published data reflected only the safety of administration by healthcare professionals.

PANEL RULING

The Panel noted that the SPC for Betaferon stated that "injection site reactions occurred frequently". The SPC for Avonex listed injection site reactions as a less common event. The statement in question, "More injection site reactions were seen with Betaferon than with 1a...", acknowledged this difference but linked it to who carried out the administration. The Panel considered that who administered the two injections might have an impact on the incidence of injection site reactions but then so might other factors such as the route of administration. Betaferon was to be given subcutaneously whereas Avonex was to be given by deep IM injection.

Overall the Panel considered that the statement was

misleading with regard to the incidence and cause of injection site reactions and ruled a breach of Clause 7.2 of the Code. It was not necessary to make any further ruling regarding the alleged breaches of Clauses 7.3 and 7.7.

4 "Questions have also been posed with regard to the dose used for 1a. Many experts believe it is too low and, in the USA, the FDA has asked for additional 1a studies to be done with double and triple the dosage used in the pivotal trial. Given this situation, there is some doubt as to whether 1a has been marketed at the most effective dose in the UK."

COMPLAINT

Biogen alleged that this statement was misleading in breach of Clause 7.2. The US FDA and the competent authorities in the European Community had made unequivocal determinations that Avonex, when used in accordance with the labelled dosage, was effective. The FDA merely noted, in the course of its review of the product licence application, that routine dose-ranging studies had not been carried out before the pivotal clinical trial was initiated, and that the optimal dose had not been determined. The SPC for Avonex stated that "the optimal dose of interferon beta-1a in MS may not have been established". Neither authority indicated that the dose was too low. The European authorities made a similar finding in respect of Schering Health Care's product: the Schering Health Care SPC stated that "The optimal dose has not been fully clarified".

RESPONSE

Schering Health Care said that as Biogen itself admitted, Avonex's SPC stated that "the optimal dose of interferon beta-1a in MS may not have been established". The EMEA had also made an additional dose-finding study a condition of the Avonex marketing authorisation and Biogen was obliged to conduct a study comparing the safety and efficacy of 30 micrograms vs 60 micrograms of Avonex given intramuscularly once weekly. In contrast, no additional dose-finding studies were demanded in the Betaferon European marketing authorization. There was absolutely no doubt, therefore , that there was uncertainty about the appropriate dosage of the product. As Biogen stated, the FDA had also noted that the optimal dose had not been determined.

PANEL RULING

The Panel noted that the statement was inaccurate. The FDA had not asked for additional la studies to be done with double and triple the dosage used in the pivotal trial.

The Panel noted that the statement in question concluded with "... there is some doubt as to whether la has been marketed at the most effective dose in the UK". The press release was silent on the matter of the optimal dose for Betaferon. The Panel noted, however, that the SPCs for both products indicated that their optimal doses had not been established. The Panel considered that giving this information for Avonex but not for Betaferon was misleading. The Panel considered that most readers would assume by implication that the optimal dose of Betaferon had been established which was not so.

A breach of Clause 7.2 was ruled.

5 "The Betaferon study was not designed to show a significant effect on progression of disability. Nevertheless a strong 'trend' towards a slowing of disease progression was observed in the Betaferon trial."

COMPLAINT

Biogen said that this statement made a claim that Betaferon had an effect on disability in multiple sclerosis. This was in direct contradiction to the SPC for Betaferon, which specifically stated that "there is no evidence of an effect on disability". Citing a benefit from a "strong trend" that was not statistically significant in this manner was highly misleading, especially in materials directed to the lay press, which could not be expected to understand that a "trend" which was not statistically significant had little or no scientific value. This statement had the potential to undermine confidence in the pharmaceutical industry and scientific research. Biogen alleged breaches of Clauses 7.2, 7.3 and 20.2.

RESPONSE

Schering Health Care submitted that this statement made no unjustified claim about Betaferon. The company believed that it was only misleading to quote a "trend" if it had failed to make clear that it was only a trend. Accordingly, as the company had stated quite clearly that the study did not show a significant effect on the progression of disability, referring to a trend was additional information which the reader would find helpful.

PANEL RULING

The Panel noted that Schering Health Care submitted that the statement in question was based on the results of a trial that showed that Betaferon had some beneficial effect in slowing disease progression. The Panel noted that the trial was not designed to show a significant effect on progression of disability. It further noted that the SPC for Betaferon stated that there was no evidence of an effect on the progression of the disease and "There is no evidence of an effect on disability". The Panel considered that it was misleading to claim, in the press release, that Betaferon had a beneficial effect on disease progression given the information in the SPC and the design of the trial. A breach of Clause 7.2 was ruled.

6 "In the clinical trials, the reduction in the relapse rate was far greater with Betaferon than with Ia - 30% compared to 18% in all patients studied. This represented an increased likelihood of remaining relapse free at two years of 94% with Betaferon compared to 46% with Ia - and an increased time to first relapse of 93% and 31% respectively."

COMPLAINT

Biogen alleged that the comparison between trial relapse

rate figures was misleading, especially because it did not compare patients treated for the same length of time. It was important to note that the approved SPC for Avonex stated that the medicine demonstrated "a one third reduction in annual relapse rate" and the approved SPC for 1b stated that 1b showed a "reduction in frequency (30%) ... of clinical relapses". The comparison made by Schering Health Care was misleading because it compared the results for all patients without regard for how long they were in the study. When a comparison was made for patients treated for two years, Avonex demonstrated a 32.2% reduction in relapse rate, compared to 33.8% for 1b. Biogen alleged breaches of Clauses 7.2 and 20.2.

RESPONSE

Schering Health Care denied that the comparison was misleading in the circumstances, as the figures were correct and it had also, for the sake of clarity, specified that both percentages quoted related to all patients studied in the respective trials. The company deliberately did not quote the 2-year relapse rate reduction for Betaferon, even though this percentage was higher (34%), in order to permit a fair comparison. The fact that the Betaferon data included patients treated for up to five years, whereas the Avonex data did not extend beyond three years, merely re-emphasised the point that Betaferon was supported by a greater weight of data than Avonex.

PANEL RULING

The Panel noted that the statement in question was very brief and seemed to infer that patients on Betaferon were almost twice as likely to be relapse free at two years compared to patients on Avonex. The statement had not been put into context with regard to the types of patient studied or the length of time they had received treatment. According to the respective SPCs the reduction in relapse rates for Betaferon and Avonex were very similar (30% vs one third after one year's treatment, respectively). The Panel considered that the brevity of the statement gave a misleading impression of the reduction in relapse rates of the two products. A breach of Clause 7.2 of the Code was ruled.

7 "Finally, disability data from the Ia study indicates that the placebo patients deteriorated much more quickly than might have been expected from natural history studies of MS.

Yet it was this level of deterioration, and the margin of difference compared to active treatment with Ia (35% of placebo patients vs 22% of Ia patients whose disability scores worsened by at least one point) that gives rise to the statistical power of this study, and hence its reported significance."

COMPLAINT

Biogen said that the statement suggested that the patients who participated in the Jacobs study were not representative, because their condition deteriorated more rapidly than would be expected from natural history studies of MS. The published literature did not support this claim; indeed, it suggested that the condition of the patients in the placebo arm of the Jacobs study, as measured by changes in certain disability scores ("EDSS" scores) after two years, did not deteriorate as rapidly as would be expected from natural history studies.

The two principal published natural history studies were Weinshenker *et al* (1991) and Myers *et al* (1993). The Weinshenker publication reported that 46% of the total patient population, and 72% of patients for the seen-from-onset subgroup, deteriorated by one EDSS point at two years. The Myers publication reports percentages up to 60%. In contrast, 35% of the patients in the placebo arm of the Jacobs study deteriorated by one EDSS point at two years.

Biogen said that the statement was not balanced or fair and alleged breaches of 7.2 and 20.2 of the Code.

RESPONSE

Schering Health Care said that the figures quoted from Weinshenker *et al* (1991) referred to patients with an EDSS score between 3 and 6; the Avonex pivotal trial, however, included patients at a much lower level of disability (EDSS 1.0 - 3.5). Similarly, Myers *et al* referred to data from patients between EDSS 1.0 - 7.0. Schering Health Care contended that the level of placebo group progression seen in the Biogen trial was more in line with studies in chronic progressive rather than relapsing remitting MS. Weinshenker *et al* (1992) reviewed progressive data from several clinical trials and quoted three studies in chronic progressive MS with progression of at least one EDSS point at two to three years of 29-41%, much in line with the Avonex placebo group (35% at two years). Many neurologists had expressed the view that the Biogen study showed unusually rapid placebo group progression for a relapsing remitting population. A recent publication from two eminent opinion leaders in the MS field (Noseworthy and Miller (1997)) also questioned whether the 1a trial included relapsing-progressive as well as relapsing-remitting patients, and highlighted the difference in placebo group deterioration between the 1a and 1b trials and the contribution that this could have made to the level of statistical significance.

PANEL RULING

The Panel observed that the treatment of MS with interferons was an emerging clinical field. According to the paper by Noseworthy & Miller the introduction of new treatments for MS had expanded the whole area and even definitions for the various clinical courses of MS had not been fully clarified. The Panel noted that the authors, in their critique of the Jacobs paper, commented that the investigators had referred to 'relapsing' MS (rather than relapsing - remitting MS) and that in theory patients with relapsing-progressive MS might have been recruited. If such patients had been disproportionately enrolled in the placebo arm of the study a false positive result might have occurred. Noseworthy & Miller pointed out, however, that the eligibility criteria would have made this unlikely and the randomisation process would have had to have failed. The Panel did not consider that the Jacobs paper had been explicitly criticised for recruiting the wrong type of patients, only that an ambiguous description of the

population could have made this possible, although unlikely.

The Panel noted that the press release effectively condemned the Jacobs paper for having the wrong type of patients in the placebo arm. The Panel considered that the evidence for this was equivocal and had only been raised as a theoretical possibility due to the definitions of the type of MS patients enrolled by the investigators. The Panel considered that the comments made about the Jacobs paper in the press release were unbalanced and misleading. A breach of Clause 7.2 of the Code was ruled.

8 Disparagement of another company's products

COMPLAINT

Biogen alleged that by the cumulative effect of Schering Health Care's specific reference to Avonex, its misleading statements and comparisons which could not be read as accurate, balanced or fair, and related violations discussed above, the press materials constituted disparagement of another company's medicines, products and activities in breach of Clause 8.1.

RESPONSE

Schering Health Care did not accept that the press release breached Clause 8.1 as there was no prohibition under the Code against making comparisons with competitor products which did not amount to unjustified knocking copy. Taken as a whole the company believed that the press release was accurate, balanced and fair, and the fact that injection site reactions and other issues which Biogen would wish to highlight had not been given prominence did not result in the press release breaching Clause 8.1. Schering Health Care said that it would be very odd indeed if press releases and other promotional material had to give equal or greater prominence to the benefits of competitor products, as seemed to be Biogen's argument.

PANEL RULING

The Panel noted that the supplementary information to Clause 8.1 of the Code allowed critical references to be made about another company's product provided that they were accurate, balanced, fair etc and could be substantiated. The Panel considered, however, that the critical references made about Avonex were not accurate, balanced or fair and that the overall effect amounted to disparagement. A breach of Clause 8.1 was ruled.

The Panel noted that material which specifically compared competitor products, such as the press release in question, must be balanced with regard to the benefits and drawbacks of both (or all) products otherwise the material would be in breach of the Code.

9 Format, suitability, and causing offence

COMPLAINT

Biogen said that by the cumulative effect of Schering Health Care's specific reference to Avonex, misleading statements and comparisons, and related breaches of the Code discussed above, in particular the statements casting doubt on the safety of an approved medicine, the press materials failed to recognise the special nature of medicines and failed to meet the high standards required of the industry. Biogen alleged a breach of Clause 9.1 of the Code.

RESPONSE

Schering Health Care denied a breach of Clause 9.1 as there had been no attempt to cast doubt on the safety of an approved medicine. The press release had the commercially and medically justifiable objectives of highlighting significant differences between two products, one of which had been on the market for just over fifteen months prior to the press release, and the other which was about to be launched. The company considered that high standards had been maintained.

PANEL RULING

The Panel noted that the Code did permit a company to issue press releases. The Panel considered that the press release in question was unusual in that its main thrust was to highlight the advantages of Betaferon and to cast doubt on Avonex. The Panel considered that given its rulings that the press release was, in parts, misleading and disparaging of Avonex, Schering Health Care had failed to maintain a high standard. The Panel therefore ruled a breach of Clause 9.1.

10 Advertising to the general public

COMPLAINT

Biogen said that the press release had been sent to the lay press. By the cumulative effect of the specific reference to Avonex, misleading statements and comparisons, and related breaches of the Code discussed above, the press release constituted advertising to the general public in breach of Clause 20.1.

RESPONSE

Schering Health Care provided a list of the editors and journalists to whom the press release was sent and pointed out that with three exceptions, all of the journals were medical, and that with the three newspapers the press release was issued to the medical editors. Schering Health Care considered, therefore, that it was slightly disingenuous of Biogen to continually refer in its complaint to the press release to the "general public" and the "lay press". The freelance journalists listed were all connected with the medical press and, while a copy was also sent to a business editor of the Financial Times, Schering Health Care did not consider that any breach of Clause 20.1 had occurred.

PANEL RULING

The Panel noted its comments regarding the distribution and content of the press release made in point 1 above. It did not accept that the press release was an advertisement to the general public and no breach of Clause 20.1 was ruled.

11 Breach of Clause 2

COMPLAINT

Overall Biogen alleged that the press release brought discredit upon and reduced confidence in the pharmaceutical industry in breach of Clause 2 of the Code.

RESPONSE

Schering Health Care denied a breach of Clause 2 on the basis that the press release was fair and accurate.

PANEL RULING

The Panel noted that it had ruled that the press release was, in parts, misleading and disparaging of Avonex. The Panel did not consider however that the press release was in breach of Clause 2 and ruled accordingly.

Complaint received **16 June 1997**

Case completed **16 September 1997**

CASE AUTH/570/6/97

E MERCK v GOLDSHIELD

Imuderm mailing

E. Merck made two allegations in relation to a mailing for Imuderm sent by Goldshield Healthcare. The Panel ruled a breach of the Code in relation to an allegation that Goldshield had failed to supply substantiation for a claim made in the mailing when requested to do so by a health professional in E Merck's employ. The Panel noted that substantiation for a claim had to be supplied to any health professional requesting it even if that health professional worked for a pharmaceutical company.

The second allegation concerned the claim "This outstanding lipid deposition seals in moisture, alleviating symptoms of dry ageing skin, eczema and psoriasis". The Panel noted that this clinical claim was referenced to a healthy volunteer study. The Panel considered that the use of a healthy volunteer study to support a clinical claim was misleading and in breach of the Code.

E Merck Pharmaceuticals submitted a complaint about a mailing on Imuderm sent by Goldshield Healthcare. The mailing consisted of a "Dear Doctor" letter and referred to Imuderm Therapeutic Oil. One paragraph in the mailing read "In an immersion study, Imuderm Therapeutic Oil gives superior lipid deposition when compared to other leading dispersible bath additives. This outstanding lipid deposition seals in moisture, alleviating the symptoms of dry ageing skin, eczema and psoriasis, (1)". The cited reference had been published in the Journal of the Society of Cosmetic Chemists in 1991.

Goldshield Healthcare was not a member of the ABPI but nevertheless responded to the complaint.

1 Refusal to provide substantiation for a claim

COMPLAINT

E Merck alleged that Goldshield had refused to provide the company, or a health professional in the company's employment, with a copy of data referenced in the promotional material. The data requested was the reference for the claim "This outstanding lipid deposition seals in moisture, alleviating the symptoms of dry ageing skin, eczema and psoriasis".

E Merck provided copies of the correspondence which commenced on 17 April when a medical information assistant wrote to Goldshield asking for a copy of the immersion study which had been referenced. The reply from Goldshield said that E Merck should be able to obtain a copy of the relevant paper as it had been able to obtain a copy of the promotional piece from a restricted mailing. Following this another member of E Merck's staff wrote to Goldshield stating that he would like a copy of the study. The headed paper used indicated that he was a pharmaceutical information specialist. In the letter he stated that he was in the process of completing a training package on emollient bath additives. The letter had been written from what appeared to be a home address in Banbury. Goldshield replied to him at Merck Dermatology and said that having established contact with his mother's address, it referred him to the original response to the request. The head of regulatory affairs at E Merck then wrote to Goldshield and said that the refusal to provide a copy of a cited reference was a breach of the Code. The response from Goldshield stated that a company of E Merck's stature should be able to obtain a copy of a paper published in a reputable journal. For this reason the company considered that it was not obliged to send a copy to a competitor. The letter from Goldshield also referred to the fact that an E Merck employee had made a request for the paper using a pretext which appeared to be not strictly correct.

E Merck alleged a breach of Clause 7.4 of the Code.

RESPONSE

Goldshield said that the mailing was sent to selected GPs on 25 March 1997. The medical information assistant of Merck Dermatology wrote to Goldshield and referred to the mailing and asked for a copy of the referenced paper. Goldshield said that realising the request came from a competitor company, which should have access to published papers about its speciality, it declined to send a copy of the paper. The company then received a letter from a pharmaceutical information scientist at a private

address in Banbury. Since the letter referred to compiling a training package on emollient bath additives, the address on the letter was contacted by phone. It was the company's policy to provide appropriate information for apparently independent, practice connected, pharmacists. The letter referred to a practice nurse. A phone call to the address revealed that the address was that of the correspondent's mother and the correspondent was an employee of Merck Dermatology. The head of regulatory affairs of E Merck wrote referring to the correspondence relating to the published paper and alleged a breach of Clause 7.4 of the Code. The response from Goldshield suggested that E Merck should have access to papers published in a reputable journal.

Goldshield pointed out that the complaint from E Merck to the Authority indicated that the complainant had obtained a copy of the study since comment was made about its contents.

Goldshield submitted that a competitor medical information assistant or an employee of a competitor company, purporting to be an independent pharmacist, were not members of the health professions or appropriate administrative staff as defined in Clause 7.4 of the Code. Clause 1.4 defined the term "health profession" as including members of the medical, dental, pharmacy or nursing professions and any other person who in the course of their professional activities may prescribe, supply or administer a medicine.

Goldshield pointed out that the therapeutic indications for Imuderm Therapeutic Oil as approved in the marketing authorization were atopic eczema, senile pruritus, ichthyosis neurodermatitis, psoriasis, eczema craquele and contact dermatitis. Clause 7.4 stated that substantiation need not be provided in relation to the validity of indications approved in the marketing authorization.

PANEL RULING

The Panel noted that Clause 7.4 required that substantiation for any information claim or comparison must be provided without delay at the request of members of the health professions or appropriate administrative staff. It was not relevant whether the health professional worked for a pharmaceutical company or was employed outside the industry. The Code made no differentiation in this respect. Companies were obliged to provide substantiation on request from a member of the health professions and if that health professional worked for a pharmaceutical company then so be it. Substantiation still had to be provided.

The Panel noted that although the cited reference had appeared in a publication and it had been possible for E Merck to acquire a copy of it, the Code required a company to provide substantiation, published or not, upon request.

The Panel noted Goldshield's submission that substantiation need not be provided in relation to the validity of indications approved in the marketing authorization but considered that this did not apply as the claim in question "this outstanding lipid deposition seals in moisture" went beyond a claim for the licensed indications. The company was therefore obliged to provide substantiation for the claim that Imuderm Therapeutic Oil had outstanding lipid deposition that sealed in moisture. This had not been done upon request from a member of the health professions. The Panel therefore ruled a breach of Clause 7.4 of the Code.

The Panel considered that it was unfortunate that E Merck had attempted to obtain a copy of the reference by using the home address of a member of its staff.

2 Claim "This outstanding lipid deposition seals in moisture, alleviating the symptoms of dry ageing skin, eczema and psoriasis"

COMPLAINT

E Merck said that the reference cited to support the claim was a healthy volunteer study. The relevant paper stated "The experiments were conducted on healthy volunteers. Dry, aged skin may show a different deposition pattern". In addition E Merck pointed out that the study did not examine efficacy in eczema or psoriasis as indicated by the claim. A breach of Clause 7.2 of the Code was alleged.

RESPONSE

Goldshield accepted that the reference number was in the wrong place. It should have appeared after the claim "In an immersion study, Imuderm Therapeutic Oil gives superior lipid deposition when compared to other leading dispersible bath additives." instead of after "This outstanding lipid deposition seals in moisture, alleviating the symptoms of dry ageing skin, eczema and psoriasis.". This change had been made in subsequent promotional items.

Goldshield submitted that the transfer of the reference number overcame the E Merck complaint. The reference was undertaken in normal healthy volunteers and in the revised text the claim about the immersion study was separated from the justified claims. The efficacy claims were in accordance with the marketing authorization for the product.

PANEL RULING

The Panel noted that the study involved only six healthy volunteers aged 18-45 and had been used as a reference to a clinical claim. The Panel noted that the paper stated that "The experiments were conducted on healthy volunteers. Dry, aged skin may show a different deposition pattern". The Panel considered that the use of the reference to support a clinical claim was misleading and therefore ruled a breach of Clause 7.2 of the Code.

The Panel did not accept Goldshield's view that repositioning the reference number would overcome the complaint as the claim, "In an immersion study, Imuderm Therapeutic Oil gives superior lipid deposition when compared to other leading dispersible bath additives", did not make it clear that the data was on healthy volunteers. The Panel requested that Goldshield be advised of its views.

Complaint received 20 June 1997

Case completed 11 August 1997

CASES AUTH/571/6/97 and AUTH/578/7/97

DOCTOR v PFIZER

Press articles on Viagra

In Case AUTH/571/6/97 a doctor complained about an article in the Daily Mail headed "Can this pill beat the great male taboo?". The article referred to the Pfizer product Viagra which was undergoing clinical trials and said that it could be available in Britain as early as next year, bringing an end to the misery of thousands of men. The complainant alleged that Pfizer had facilitated and encouraged the publication of numerous articles in national newspapers and magazines which actively promoted Viagra. Such therapy could induce unacceptable cardiovascular effects but this point had been suppressed and accordingly it was misleading, biased and potentially damaging.

The Panel examined materials supplied by Pfizer to the Daily Mail journalist concerned, noting that articles in the press were judged on the materials supplied and not on the articles themselves. It was not necessarily a breach of the Code to include brand names in material intended for the press. The Panel did not consider that the information provided by Pfizer constituted an advertisement and accordingly ruled no breach in that regard. The Panel considered that a press release supplied to the journalist was not presented in a balanced way and ruled it in breach.

Case AUTH/578/7/97 was a complaint from the same doctor about a further article which had appeared in the Daily Mail which had a headline "Wonder drug may go on sale next year". The Panel noted that Pfizer had been unable to trace any contact with the author of the article who was said in the article to be in New York. The article did not appear to be based on the materials at issue in Case AUTH/571/6/97. No breach was ruled.

Case AUTH/571/6/97

A doctor complained about a one page feature on male impotence which appeared in the Daily Mail on 17 June 1997. The page was headed "Can this pill beat the great male taboo?". The main article referred to the Pfizer product Viagra which was undergoing clinical trials. The article said the product could be available in Britain as early as next year, bringing an end to the misery of thousands of men. The feature page ended with the telephone number of The Impotence Association Helpline.

COMPLAINT

The complainant alleged that the article was in breach of the Code. He said that over a lengthy period of time Pfizer had facilitated and encouraged the publication of numerous articles in national newspapers and magazines which actively promoted Viagra, an unlicensed medicine for treatment of male erectile dysfunction. The complainant stated that he had received requests from numerous patients who had read the reports asking for information and requesting prescriptions.

The complainant stated that the campaign by Pfizer and its public relations advisers culminated in a four page promotional presentation in the Daily Mail of 17 June. In the complainant's view, this was nothing less than blatant promotion to create patient-led demand for a prescription only medicine ahead of its marketing release.

The complainant pointed out that the article promoted the brand name Viagra no less than nine times and anticipated the granting of a marketing authorization by the Medicines Control Agency. As Viagra was a potent cardiovascular medicine and its function in the treatment of male erectile dysfunction was but an observed, associated effect, it was by no means certain that the MCA would grant a marketing authorization for the product, as such therapy could induce unacceptable cardiovascular effects. This point was suppressed in all Pfizer's articles and accordingly, it was misleading, biased and potentially damaging.

RESPONSE

Pfizer said there was no basis for the allegations that Pfizer had facilitated and encouraged the publication of numerous articles in the lay media to actively promote Viagra and that the activities were nothing less than blatant promotion to create patient-led demand for a prescription only medicine ahead of the planned marketing authorization. The company accepted that there had been a considerable amount of media coverage of the product in the UK but this had been generated by the nature of the product and the condition for which it had been tested in clinical trials. Pfizer had not actively generated such coverage and had been concerned to put into perspective a subject of wide public interest.

Pfizer explained the background to the product, which had been tested in clinical trials for the treatment of male erectile dysfunction (MED), commonly referred to as impotence. MED was a condition affecting up to one in ten adult males and could be caused by a variety of medical conditions, including diabetes, multiple sclerosis and treatment for high blood pressure. MED caused a great deal of distress, embarrassment and even depression. The condition often led to strained relationships. Although some men sought treatment, many others suffered in silence because of shame or embarrassment and others might not be aware that treatment existed. Pfizer's product Viagra was originally developed for treatment for angina. It was first given to healthy male volunteers in 1991. As a result of these early studies, some of the volunteers reported increased erections. At about the same time, publications in prominent scientific journals revealed new information about the mechanisms causing erection of the penis. Thus the company decided to investigate it further. In 1993 and 1994, two small pilot clinical trials were carried out. The preliminary results indicated that Viagra increased the patient's ability to get erections in response to sexual stimulation. In October 1994, the results were publicly disclosed by Pfizer Limited's US parent company, Pfizer Inc, to Wall Street analysts as part of a disclosure of the status of Pfizer's compounds in development. A copy of Pfizer Inc's news release, dated 24 October 1994, which referred to the product as UK92,480 was provided. The release was not targeted at UK media as such, although Pfizer understood it was sent to the New York bureau of

Scrip and the Financial Times, PR Newswire in the US (which had European Services), wire services such as Reuters and Associated Press and other publications which had asked to be put on the Pfizer Inc press release mailing list, namely Market Letter Publications Ltd, OTC Publications Ltd, Chemistry in Britain, MDIS Publications, UK Offices of Scrip and the Financial Times and European Chemical News.

Pfizer submitted there followed from then and to the present time considerable media interest in the compound because of the nature of the condition and the fact that if the product was licensed, it would be the first oral treatment. The subject was of continuing public interest and media coverage, much of which unfortunately trivialised the condition and its treatment.

At the end of 1994, Pfizer in the UK received several enquiries generated by a Daily Telegraph article. To respond to these enquiries, the company issued a press release dated 21 December 1994. Although entitled "Press Release", it was in fact a press statement sent in response to those media which had asked for comment, including local and regional radio and press, Daily Express, Daily Telegraph, and Sunday Mirror. Pfizer drew attention to the statement in the press release that "this new medicine could fail during this period of research, for reasons such as lack of established efficacy". Dealings with the media in respect of the product by Pfizer in the UK had been solely reactive. Numerous media calls, sometimes requesting interviews, had been received. Staff responding to the media had explained the product was still in development and was not available to patients. Similarly, members of the public who asked about the product had been advised that it was in trials and that they should talk to their own doctors about their condition and its treatment. They might also be referred to The Impotence Association.

Pfizer Inc in the US had issued one other press release, dated 6 May 1996, addressing Viagra. It referred to significant results reported at a scientific meeting in the US. As was the case with the 24 October 1994 press release, it was not targeted at non-US media although Pfizer understood that it was sent to the UK media mentioned in relation to the press release dated 24 October 1994. Viagra had also been mentioned in other Pfizer Inc press releases as part of releases on such matters as the annual financial results and the status of the company's research and development programme. On occasion, the 6 May 1996 press release had been passed to the UK media in response to specific requests for information about the product.

Pfizer submitted that there had been considerable interest in the product and much media coverage in the UK and elsewhere. The complainant had apparently seen UK coverage but had wrongly concluded that it was actively generated by Pfizer. This was not the case, Pfizer had not generated that coverage and, in particular, had not employed any public relations firm to advise on or implement any such active strategy. Pfizer had not been associated with the Impotence Association or any other bodies for such purposes.

With regard to the article in the Daily Mail of 17 June 1997, the author, Angela Brooks, rang Pfizer at Sandwich and spoke to the public relations department. The contact was not initiated by Pfizer, directly or indirectly. There were conversations over a number of days, during which Ms Brooks asked about the clinical trials of Viagra and its status generally and pressed for as much information as possible, including the names of patients and investigators. The company refused to provide any patient contact, nor was any investigator specifically mentioned by the company, although it did agree to provide publicly available data. It was stated that the product was still in development, not licensed for prescription and thus not available to patients.

Pfizer submitted that in the absence of key personnel at the company when the need to respond became more urgent, the public relations department referred the request for publicly available information to their US colleagues who suggested that it provided a copy of the Pfizer Inc press release of 6 May 1996 and some abstracts of clinical trials. Those documents were sent to the author. Just before publication, the author asked about regulatory submissions in the US and UK, and was told that they would be made later in this year and it could not speculate about exact approval times. It could take 12 to 18 months in the UK.

With regard to the complainant's allegations that the article, and thus Pfizer, anticipated the granting of a marketing authorization for the product and that it suppressed the fact that such authorization was by no means certain, Pfizer submitted that the information it had provided did not lead to that conclusion. It had explained that the product was not approved and the optimistic remarks by Dr Lue, in the Pfizer Inc press release of 6 May 1996, included the caution "if further clinical trials prove its efficacy and safety ..."

Pfizer noted that the Daily Mail article referred to Dr Gingell and to The Impotence Association. It had not referred Ms Brooks to Dr Gingell specifically, although his name appeared in the abstracts of clinical trials provided by the company. The Impotence Association was entirely independent of Pfizer and it did not provide it with sponsorship. Pfizer was not a member of The Impotence Association, although one of its employed doctors had joined as an individual member. The company had had contact with The Impotence Association because it was convenient and appropriate to refer to The Impotence Association certain members of the public who approached the company for advice. Pfizer advised The Impotence Association about the status of the product and understood that its officers had specialist knowledge in the field, in some cases derived as clinical trialists. Pfizer gave The Impotence Association no encouragement, directly or indirectly, to promote interest in the product. Indeed, it was anxious that if The Impotence Association discussed Viagra, it should emphasise that the product was only at the development stage.

PANEL RULING

The Panel noted that Pfizer UK had supplied information to the journalist at the Daily Mail. Pfizer in the US had suggested that Pfizer UK supply the journalist with a Pfizer Inc press release, 6 May 1996, and abstracts of clinical trials.

The Panel considered that the information supplied by Pfizer to the Daily Mail journalist, a UK publication, came

within the scope of Clause 20 of the Code. It was irrelevant whether the information had been supplied by the US or by the UK company. The UK company was responsible under the Code.

The Panel noted that the press release of 6 May 1996 mentioned the outcome of clinical trials and included the quotation "If further clinical trials prove its efficacy and safety, it may be a dream come true for many patients who are looking for a magic pill to improve their erection". The press release said that the oral medicine was in the late stage of development.

The Panel noted that complaints about articles in the press were judged on the information provided by the pharmaceutical company or its agent to the journalist and not on the content of the article itself. It was not necessarily a breach of the Code to include brand names in materials for the press.

The Panel accepted the company's submission that the coverage was not actively generated by Pfizer. It noted Pfizer's submission it had not employed any public relations firm to advise or implement on such a strategy.

The Panel did not accept that the information provided by Pfizer constituted an advertisement and ruled no breach of Clause 20.1 of the Code.

The Panel noted the requirement of Clause 20.2 of the Code, that information about medicine which is made available to the general public either directly or indirectly must be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. The Panel considered that the 6 May 1996 press release provided to the journalist was not presented in a balanced way and therefore ruled a breach of Clause 20.2.

Case AUTH/578/7/97

This case concerned an article that appeared in the Daily Mail, 10 July 1997. The article was headed "The Good Love Pill" with a subheading "Wonder drug may go on sale next year". The article referred to Viagra. It also referred to early clinical trials with women.

COMPLAINT

The complainant pointed out that, since he had complained about the Daily Mail article of 17 June 1997, Pfizer's unlicensed product Viagra had again featured in the Daily Mail in a half page article. It featured the brand name and the claim that it "could be available in Britain as early as next year". This statement, together with the headline "Wonder drug may go on sale next year", clearly anticipated MCA licensing approval, which was by no means a foregone conclusion.

RESPONSE

Pfizer submitted that having made enquiries within Pfizer in the UK and at headquarters in the United States and Brussels, it could not trace any contact by Pfizer or representatives of Pfizer with staff of the Daily Mail in connection with the preparation of the article of 10 July 1997.

Pfizer referred to its more detailed comments on the matter in the response to the complaint in Case AUTH/571/6/97.

PANEL RULING

The Panel noted that Pfizer UK had been unable to trace any contact between Pfizer and the author of the second article Philip Finn who, according to the article was in New York.

The Panel noted that the article did not appear to be based on the information provided by Pfizer submitted in Case AUTH/571/6/97. The article referred to the effect of Viagra on women. No mention was made in the Pfizer materials of effects on women.

Given the submission from Pfizer and the content of the article, the Panel ruled that there was no breach of the Code.

Case AUTH/571/6/97	
Complaint received	**23 June 1997**
Case completed	**4 September 1997**
Case AUTH/578/7/97	
Complaint received	**11 July 1997**
Case completed	**8 September 1997**

CASE AUTH/573/6/97

HOSPITAL DOCTOR v ORGANON

Puregon "Dear Doctor" letter

A hospital doctor complained about a "Dear Doctor" letter on Puregon (follitropin β) which had been sent by Organon. The letter included a table which compared the costs of a Puregon ampoule 50 IU (£21.10) and a follitropin α ampoule 75 IU (£29.17). The letter stated that it may be appropriate to give a lower dose of Puregon. The complainant was concerned that Organon was promoting the equivalence of Puregon 50 IU to 75 IU of follitropin α. He considered that such misleading information might lead to inappropriate dosage selection, thus compromising the outcome of treatment, and might also increase the costs of treatment.

The Panel considered that the letter was confusing as the table compared the costs of the smallest ampoules of Puregon and follitropin α although the basis of the comparison had not been stated. The Panel considered that it would not be unreasonable for some readers to relate the lower doses of Puregon referred to in the text to the ampoule sizes referred to in the table and assume that a dose of Puregon of 50 IU was equivalent to follitropin α 75 IU. The Panel considered that the table was misleading as alleged. The starting dose of Puregon was usually 75 IU or higher but the impression given was that 50 IU was a recommended dose as opposed to the smallest ampoule size. A breach of the Code was ruled.

A hospital medical director complained about a "Dear Doctor" letter on Puregon (follitropin β), a recombinant follicle stimulating hormone (FSH). The letter had been sent by Organon Laboratories Ltd.

The letter referred to the fact that Ares Serono had written to all hospital prescribers advising them to use its recombinant FSH (follitropin α) as its human FSH, urofollitrophin HP, would not be available for a period of time in the primary care sector. The letter included a table which compared the costs of a Puregon ampoule 50 IU (£21.10) and a follitropin α ampoule 75 IU (£29.17). The letter stated that there was a significant difference in the cost of the two recombinant products. Underneath the cost comparison table was the following extract, printed in bold, from the Puregon summary of product characteristics (SPC) "Studies have shown that Puregon (follitropin β) 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 dose 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 IU and 100 IU".

COMPLAINT

The complainant was concerned that Organon was promoting the equivalence of Puregon 50 IU ampoule size to the 75 IU ampoule size of follitropin α. The complainant did not dispute a statement in the letter that Puregon was shown to be superior to urinary FSH. The complainant was unaware of any data in the literature to substantiate the statement "Therefore it may be appropriate to give a lower dosage of Puregon than for urinary FSH". To take that one step further and infer that it was reasonable to use 50 IU of Puregon rather than 75 IU of follitropin α seemed to be flagrantly misleading and had presumably been used because on a unit for unit basis Puregon was clearly much more expensive (£31.65 versus £29.17).

The complainant was very concerned that such misleading information might lead to inappropriate dosage selection for patients thereby compromising the outcome of treatment and might also increase the costs of treatment.

RESPONSE

Organon submitted that the statement as it appeared in the "Dear Doctor" letter "Therefore it may be appropriate to give a lower dosage of Puregon than for urinary FSH" was a direct quote from the SPC. The information and warnings in the SPC were a result of clinical data submitted and assessed during the licensing of the product. One of these studies was the single, largest prospective clinical study carried out in IVF comparing recombinant FSH (Puregon) with urinary FSH. In total 585 subjects received recombinant FSH (Puregon) and 396 urinary FSH (Metrodin) for ovarian stimulation.

Organon submitted that the aim of stimulation was to increase the number of oocytes for assisted reproduction. Therefore the number of oocytes retrieved was chosen as one of the main efficacy parameters in the study. The results showed that a significantly higher number of oocytes was retrieved in the recombinant FSH group and that recombinant FSH had higher potency compared to urinary FSH.

Organon stated that one of the great risks of infertility treatment was the possibility of overstimulation of the ovaries leading to the syndrome of ovarian hyperstimulation (OHSS). This potentially life-threatening complication could be avoided by tailoring the dose of FSH administered to each patient based on regular monitoring of follicle development and plasma oestradiol levels.

The statement "...therefore it may be appropriate to give a lower dosage of Puregon than for urinary FSH" was not a promotional statement in the SPC. It was a warning to doctors that it might be advisable to administer a lower dosage of Puregon because it had been shown to be more potent than urinary gonadotrophins. By starting with a lower dose the risk of overstimulation of the ovaries was reduced. Furthermore, the SPC and the "Dear Doctor" letter stated that "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 IU and 100 IU". This implied that in some cases it might be appropriate to start with a lower dose of

Puregon in the interest of patient safety. In the clinical situation the lower strength of 50 IU was a benefit because it increased the flexibility of dosing while retaining the maximum safety advantage for the patient.

Organon submitted that the letter did not infer that it was reasonable to use 50 IU Puregon instead of 75 IU follitropin. Organon's position was that it believed that the lower strength of 50 IU was beneficial to the doctor as it allowed more flexibility with respect to dose selection. In keeping with the principle of giving the lowest effective dose doctors now had the choice of commencing treatment with 50 IU. The SPC reflected this with the statement "Therefore it may be appropriate to give a lower dosage of Puregon than for urinary FSH".

Dosage selection in infertility treatments was a very complex area and the dose was tailored specifically to the needs of the patient. Therefore the company hoped that the 50 IU strength would give a doctor extra flexibility and perhaps reduce unnecessary wastage.

The current UK prices of the two recombinant preparations were shown in the "Dear Doctor" letter. The comparison did not suggest that 50 IU Puregon and 75 IU follitropin were equivalent. The letter compared the prices of the lowest strength of each preparation. This was not a price comparison of dosage cost nor was it a comparison of the cost of a treatment cycle. As Organon did not have a 75 IU preparation currently available, the company was unable to compare the prices of preparations of the same strength.

Organon submitted that it would not expect or propose that any doctor treating a patient for infertility would make a dosage selection based on the contents of the letter. Any doctor involved in infertility knew that it was a complex area with respect to dosage selection. Careful dose selection and monitoring of patients was crucial for the successful outcome of treatment.

The statement taken from the SPC (quoted in the letter) acted merely as a warning to a doctor that he/she should be aware that Puregon had been proven to be more potent than urinary gonadotrophins. The company hoped that a doctor would err on the side of caution and not rely too heavily on past experience with urinary gonadotrophins and thus risk giving too high a dose putting their patient at an unnecessary risk of a life-threatening condition (OHSS).

PANEL RULING

The Panel noted that Puregon was indicated for use in anovulation and controlled ovarian hyperstimulation to induce multiple follicles in medically assisted reproduction programmes. The Panel noted that the SPC stated that in comparative clinical studies with Puregon and urinary FSH it had been shown that Puregon was more effective than urinary FSH in terms of a lower total dose and a shorter treatment period to achieve pre-ovulatory conditions. Therefore it might be appropriate to give a lower dose of Puregon than for urinary FSH. The recommended dose in anovulation was usually to start with a daily administration of 75 IU. If there was no response then the dose was gradually increased. For controlled ovarian hyperstimulation the recommended starting dose was 150 - 225 IU with a maintenance dose of 75 - 375 IU.

The Panel noted that follitropin α (Gonal F; Serono: ref ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1996-97) was only indicated in assisted reproduction technologies with a recommended starting dose of 150 - 225 IU. It appeared to the Panel that in the only indication in which the two could be directly compared the starting doses for Puregon and follitropin α were identical.

The Panel considered that the letter was confusing in that the table compared the costs of the smallest ampoules of Puregon (50 IU) with follitropin α (75 IU) although the basis of the comparison had not been stated. The emboldened text below the table compared the efficacy of Puregon with urinary FSH. The Panel considered that, given the juxtaposition of the table and the text, it would not be unreasonable for some readers to relate the lower doses of Puregon referred to in the text to the ampoule sizes referred to in the table and assume that a dose of Puregon 50 IU was equivalent to follitropin α 75 IU.

The Panel noted that the table showed a cost difference of £8.07 in favour of Puregon whereas on a unit for unit basis Puregon was more expensive than follitropin α.

The Panel considered that the comparison of the cost of Puregon 50 IU with follitropin α 75 IU was misleading as alleged. According to the SPC the starting dose for Puregon was usually 75 IU or higher depending on the indication. The impression given by the chart, however, was that 50 IU of Puregon was a recommended dose, as opposed to the size of the smallest available ampoule, and that this was equivalent to a dose of 75 IU of follitropin α. The Panel ruled a breach of Clause 7.2 of the Code.

Complaint received **23 June 1997**

Case completed **11 August 1997**

CASE AUTH/576/7/97

NO BREACH OF THE CODE

HOECHST MARION ROUSSEL v SERVIER

Use of trough:peak ratios in promotion of Coversyl

Hoechst Marion Roussel complained about a journal advertisement for Coversyl (perindopril) issued by Servier.

It was alleged that a claim "Trough/peak ratio of 87-100%" was a selective quotation from the available literature for trough:peak (T:P) ratios for perindopril, did not represent a balance of opinion on the topic and was misleading. The methodology for calculating the T:P ratio of an antihypertensive medicine had never been defined and the literature contained widely disparate values for individual medicines.

The Panel noted that T:P ratios were regarded by some as useful indicators for determining or confirming dosage intervals for antihypertensive medicines. There was evidence that the T:P ratio for perindopril was between 87 and 100% although some lower figures appeared in the literature. Given the difficulty in determining definitive values for T:P ratios and the available data, the Panel did not consider that the range of 87-100% for perindopril given in the advertisement was misleading. No breach of the Code was ruled.

Hoechst Marion Roussel also alleged that the prominent use of T:P ratios in promotional activities *per se* breached the Code with regard to supplementary information to the Code which stated that "Where a clinical or scientific issue exists which has not been resolved in favour of one generally accepted viewpoint, particular care must be taken to ensure that the issue is treated in a balanced manner in promotional material". The T:P ratio was an inappropriate and unvalidated variable with which to infer merit of an ACE inhibitor. Prominent usage of T:P ratios in promotional material misled the prescriber into believing that this variable was somehow a reliable and predictable indication of clinical outcome when no such relationship had been established.

The Panel noted that the only example of the use of T:P ratios in relation to Coversyl that it had been provided with was in the advertisement the subject of complaint. In that advertisement the Panel did not accept that the claim regarding the T:P ratio for perindopril was being used as a marker of clinical efficacy and no undue significance had been attached to it. In the Panel's view, the claim informed prescribers that the T:P ratio for perindopril was such as to make the product suitable for a once daily dosage regimen. No significance was attached to its magnitude. There was no actual or implied comparison with other ACE inhibitors. The Panel considered that the use of the T:P ratio in the advertisement was not misleading and no breach of the Code was ruled.

Hoechst Marion Roussel Ltd complained about a journal advertisement (C96.1.A) for Coversyl (perindopril) which had been issued by Servier Laboratories Ltd. The first claim in the advertisement was "Trough/peak ratio of 87 - 100%" for which two supporting references were given, Morgan *et al* (1992) and Morgan *et al* (1993). There was a second claim "4 mg dose controls 77% of patients" which was referenced to a paper by Fressinaud *et al* and finally the strapline "A practical once daily ACE inhibitor *one* 4mg *tablet daily*".

1 Claim "Trough/peak ratio of 87 - 100%"

COMPLAINT

Hoechst Marion Roussel alleged that the advertisement was in breach of Clause 7.2 of the Code as the selective quotation from the available literature for trough:peak (T:P) ratios for perindopril did not represent a balance of opinion on this topic. On consulting an expert in the area, with specific reference to the literature referred to by Servier, the following observations could be made:

The methodology for calculating the T:P ratio of an antihypertensive medicine had never been defined by the Food and Drugs Administration (FDA) in the US. Thus, by virtue of differing methodologies, and for other reasons, the published literature often contained widely disparate values for individual medicines and it was therefore necessary, in the absence of an appropriately designed and definitive study, to refer to all available publications to provide the reader with an accurate and honest view of the current state of scientific knowledge.

With particular respect to the T:P ratio for perindopril, there appeared to be a deliberate, and potentially misleading, selective presentation in the promotional literature of data from studies which were by no means definitive For example, from a comparison of perindopril, enalapril and captopril it was reported that perindopril had a T:P ratio of 87% (Morgan and Anderson (1993)). However, from the data available in this abstract, which was not a full paper in a peer-reviewed journal, the peak effect of perindopril, arbitrarily constrained to be four hours post dose, was 1.6mmHg for "corrected" diastolic BP, whereas the trough reduction was 11mmHg.

Thus, because the trough BP reduction was actually greater than the peak BP reduction, the T:P ratio could be calculated as 687.5%! This surely highlighted the shortcomings of the methodology employed in this particular study. However to justify their alternative calculation, the authors of this abstract stated "With perindopril there was no acute fall in BP implying that the (BP lowering) effect was maintained.....". Such an inference clearly could not be substantiated by the data presented and could not be considered to constitute a definitive analysis, particularly for the purposes of accurate quantification.

The same assumption that there must be a persisting antihypertensive effect arose in the second study which also failed to demonstrate a significant early or peak BP reduction again using the simplistic strategy of inserting single dose placebo into the treatment regimen (Morgan and Anderson (1992)). In this study, however, it was possible to refer to the baseline/pre-treatment values to calculate a ratio of 78%. Again, however, there was no justification for spuriously augmenting this value with data inferred from the single dose placebo substitution. This latter approach to methodology fell outside any

recommendations or commentary of the FDA.

The basic methodological problem with both of these studies was the absence of an appropriate placebo treatment: thus, it was impossible to calculate accurately how much of the apparent blood pressure response was attributable to the medicine itself. If the blood pressure response could not be quantified accurately then it followed that the T:P ratio could not be quantified accurately. It was one of the fundamental components of the FDA guidelines that the blood pressure responses should be assessed at "steady state". Neither of the above studies employed a parallel, or crossover, group with steady state placebo responses. Their measured, steady state blood pressure responses could, therefore, only be derived from comparisons with baseline or pre-treatment measurements, as a substitute for "steady state" placebo treatment, which would invariably lead to an over-estimate of the medicine's effect.

Finally, for the purposes of meaningful data presentation, it was recommended that a range of values should be quoted for each T:P ratio study, and these were not available in the above references. Therefore, in the absence of an inter-individual range of values from each study population, it was factually incorrect to represent summarising mean values from two different populations, each previously identified to contain only ACE inhibitor "responders", as if these two studies could define precisely the range of values for the population at large.

In contrast, on the basis of the available information, and on the basis of a reasonable interpretation of the data accessible via the published literature, only one of these studies was eligible (Morgan and Anderson (1992)). The only other available study reported a value of 35% (Zannad *et al* (1996)). This could not be considered a definitive report, but it should be quoted in any review.

In summary, an objective presentation of the T:P ratio values for perindopril based on literature at the time of appearance of the advertisement would be as follows: "Trough:peak ratios of 35% or 78% have been reported from two different studies". In addition, Servier itself suggested that lower values of T:P ratio for perindopril could be supported (Mollinedeo (1997)).

Hoechst Marion Roussel appreciated that further work had been published recently which might add more data to the debate (Myers *et al* (1996)), but this had appeared later than the advertisement in question and further served to support point 2 below.

RESPONSE

Servier referred to six publications which included a reference to the T:P ratio of perindopril.

i) Morgan and Anderson (1993): This abstract gave the results of a study comparing the effects of perindopril, enalapril and captopril on blood pressure over 24 hours. Each medicine was compared at steady state with a single dose placebo. Mean figures were given for corrected diastolic blood pressure reduction at 2, 3, 4 and 24 hours. The T:P ratio for perindopril was calculated as 87%.

Servier submitted that it was considered standard practice to calculate a mean T:P ratio by first calculating individual T:P ratios from individual BP data and then calculating the mean value. Mean T:P ratio could not be calculated from mean BP data. It was therefore not possible to attempt, as Hoechst Marion Roussel had done, a re-calculation of T:P ratio using the mean BP data in this abstract.

Servier acknowledged that the methodology for calculating T:P ratio had never been defined by the FDA. The FDA did not specify a steady state placebo response. It was accepted that a formal placebo assessment was vital. In this study a formal assessment was carried out after a single dose placebo and the BP reductions corrected accordingly.

ii) Morgan and Anderson (1992): This compared the effects of perindopril and enalapril (at steady state) on blood pressure at trough and peak. The data was corrected for circadian variation and placebo response using data from a single dose placebo. The same comments about placebo assessment above applied here. The uncorrected T:P ratio for perindopril was 78%. It seemed illogical to argue that this figure should be quoted, in preference to the corrected figure of 100%, which took into account circadian rhythm and placebo effect.

Servier noted that Hoechst Marion Roussel criticised the absence of a range of values. However, a mean value of 100% could only be produced by a narrow range. It followed therefore that individual values must have been close to 100%. Servier noted that this was one of the papers which Hoechst Marion Roussel considered to be eligible to be quoted.

iii) Myers *et al* (1994): This review paper referred to unpublished data from a study of 158 patients in which the T:P ratio for perindopril 2, 4 and 8mg was reported as 100%, 100% and 95% respectively. The authors pointed out that these data must be considered preliminary.

These data which supported a T:P ratio for perindopril of 95 - 100% had been submitted to the FDA and were the basis for the statement in the US Monograph for perindopril, approved by the FDA in December 1993, "After 2 - 16mg doses of perindopril the trough mean systolic and diastolic blood pressure effects were approximately equal to the peak effects (measure 3 - 7 hours after dosing). Trough effects were about 75 - 100% of peak effects" (75% related to 16mg, an unlicensed dose in the UK).

iv) Myers *et al* (1996): In this study, after a four week placebo run-in, 193 patients were randomised to receive 2, 4, 8 or 16mg of perindopril or placebo for 12 weeks. Trough and peak effects in diastolic blood pressure were determined. The study, which addressed any issue of appropriate placebo control, gave T:P ratios for perindopril 2, 4, and 8mg was 100, 100 and 97% respectively. The T:P ratio for 16mg was 74%.

v) Zannad *et al* (1996): This paper did not present any original data. It was a comparison of T:P ratios of ACE inhibitors based on a retrospective literature analysis. Briefly, the methodology involved selection of all published papers on 24 hour ambulatory blood pressure monitoring with an ACE inhibitor which included hourly mean values of systolic BP and diastolic BP. For each study, the magnitude of diastolic BP changes were

calculated from mean values on active treatment and placebo. The curve was reconstructed and smoothed using a polynominal regression best fit procedure. The T:P ratio was then calculated. In the case of perindopril, only one study (Santoni *et al* (1989)) fulfilled Zannad's criteria. This was a study of pulse wave velocity and ambulatory blood pressure measurement in which T:P ratio was not calculated. Based on recalculations of the data in this study, Zannad stated a T:P ratio for perindopril of 35%.

There were numerous criticisms of the Zannad study; for example, it was not a clinical trial but a retrospective literature analysis, values were extrapolated from an average curve, and T:P ratio was derived from mean values, not individual values.

Servier pointed out that the Zannad study had been referred to in a previous case (Case AUTH/312/6/95). The Panel had considered that it 'could be criticised as the scientific relevance was open to question and the methodology was at odds with current requirements'. There had been no developments since 1995 to justify changing this view. Servier submitted that the T:P ratio value for perindopril from this publication was not sound and should not be referred to in any scientific review of T:P ratio.

vi) Zannad (1993): This was a second publication of the same analysis, although here still using only the Santoni study, the T:P ratio for perindopril was given as 30%.

In summary, Servier said that a review of the available literature gave values for the T:P ratio of perindopril of 87% (Morgan and Anderson (1993)), 100% (Morgan and Anderson (1992)), 95 - 100% (Myers (1994)) (provisional data) and 97 - 100% (Myers *et al* (1996)). Servier considered that the statement "T:P ratio of 87 - 100%" accurately reflected this, represented a true balance of opinion and was not in breach of the Code.

PANEL RULING

The Panel noted that T:P ratios were regarded by some as useful indicators for determining or confirming dosage intervals for an antihypertensive medicine. The US Monograph for perindopril, approved by the FDA, made reference to T:P ratios. Lack of a prescribed methodology for measuring T:P ratios, however, meant that the figures quoted in various papers could not be taken as definitive. The Panel noted that there was evidence that the T:P ratio for perindopril lay between 87 and 100% although lower figures did exist in the literature. A T:P ratio of 75 - 100% was given in the US Monograph for perindopril but the lower figure was related to the 16mg dose which was an unlicensed dose in the UK. In addition Zannad *et al* (1996), in a retrospective literature analysis of studies meeting various inclusion criteria, quoted a figure of 35% from one study but stated that "Additionally, some findings contrast with those based on alternative methodology, such as in the case of perindopril and the trough/peak ratios of ACE inhibitors approved by the FDA following the formulation of their new guidelines are higher than those reported in the studies analysed in this review".

The Panel noted the comments that it had made in the previous case, Case AUTH/312/6/95, related to the Zannad (1993) paper. In that case that Panel had noted that Zannad (1993) had commented in relation to the T:P ratio for perindopril that figures in excess of 50% had been reported elsewhere and thus the lower figure [30%] could be the result of unsatisfactory methodology.

The Panel did not consider that, given the difficulty in determining definitive values for T:P ratios and the available data, the range of 87 - 100% for perindopril given in the advertisement was misleading. No breach of Clause 7.2 of the Code was ruled.

2 Use of trough/peak ratios

COMPLAINT

Hoechst Marion Roussel alleged that the prominent use of T:P ratios in promotional activities *per se* further breached Clause 7.2 with particular reference to the supplementary information regarding emerging clinical or scientific opinion. This stated that "Where a clinical or scientific issue exists which has not been resolved in favour of one generally accepted viewpoint, particular care must be taken to ensure that the issue is treated in a balanced manner in promotional material".

T:P ratios were used by the FDA in their assessment of dosage intervals for ACE inhibitors; the Medicines Control Agency did not rely on T:P ratios but rather on clinical evidence of 24-hour blood pressure control. In quoting T:P ratios even the FDA, in stating a minimum of 50% in support of a once daily dosage, did not suggest that values above 50% were somehow more beneficial.

Hoechst Marion Roussel alleged that prominent advertising of T:P ratios and discussion of these with clinicians by representatives of Servier was designed to mislead the prescriber into believing that the T:P ratio was a marker of clinical efficacy. The promotion suggested that perindopril had a more robust claim to efficacy with once daily dosing than other ACE inhibitors licensed for once daily use for which lower T:P ratios had been reported.

In summary, Hoechst Marion Roussel alleged that the T:P ratio was an inappropriate and unvalidated variable with which to infer merit of an ACE inhibitor. Measurement of T:P ratios was fraught with methodological difficulties, the complexity of which was impossible to reflect in the course of an interview between a representative and a prescriber and within simplistic promotional material. Prominent usage of T:P ratios in promotional material misled the prescriber into believing that this variable was somehow a reliable and predictable indicator of clinical outcome when no such relationship had been established.

RESPONSE

Servier noted that Hoechst Marion Roussel had alleged that prominent use of T:P ratio:

(i) was in breach of Clause 7.2 with particular reference to "emerging clinical or scientific opinion"

(ii) was designed to mislead the prescriber into believing that the T:P ratio was a marker of clinical efficacy

(iii) suggested that perindopril had a more robust claim to efficacy with once daily dosing than other ACE inhibitors licensed for once daily use for which lower T:P ratios had been reported.

In answer to these points Servier submitted:

(i) That the T:P ratio and its application to the development of medicines had been a topic of scientific interest since 1988, when the FDA prepared a draft document recommending a minimum T:P ratio of 50 - 67%. Since then nearly 300 articles had been published, 29 of these specifically on ACE inhibitors. There was still considerable discussion about methodology. Despite this, T:P ratio was considered a relevant characteristic of an ACE inhibitor. In a recent educational article on hypertension in 'The Pharmaceutical Journal' (Sani (1997)), a table entitled "Characteristics of ACE inhibitors" included T:P ratios alongside time to maximum effect, half-life etc (the T:P ratio values quoted in this table were derived from Zannad and had been criticised by Servier (Mollinedo (1997)) and by Hoechst Marion Roussel (Desai (1997))).

Servier thus submitted that the T:P ratio was a valid characteristic to discuss in the promotion of an ACE inhibitor.

(ii) Servier submitted that the T:P ratio was a marker of clinical efficacy to the extent that it was a measure of the duration and consistency of action of an ACE inhibitor.

"When the Trough:peak ratio approaches 100% it suggests that the [medicine] produces a consistent level of effect throughout its dosage interval and is likely to be suitable as a once daily treatment for all patients" (Elliot and Meredith (1995)).

"A satisfactory (high) Trough:peak ratio indicates that the drug will provide consistent BP control throughout 24 hours. This control is important for several reasons:

- in comparison with clinic or casual BP measurements, the blood pressure values derived from 24 hour measurements are more closely correlated with a number of different indices of cardiovascular target organ damage
- cardiovascular events, which cluster in the early morning periods (corresponding in once-daily regimens to the time immediately before dosing) occur approximately 24 hours post-dose
- BP variability itself may be an important determinant of target organ damage, independent of the level of BP" (Elliot and Meredith (1996)).

Servier noted that the SPC for perindopril stated (under 'Pharmacodynamic Properties'), "Systematic Hypertension - efficacy is sustained throughout the 24 hour cycle".

Servier said that the claim in question "Trough/peak ratio of 87 - 100%" conveyed to the prescriber that perindopril, once daily, provided consistent blood pressure control throughout the 24 hour cycle. This was a relevant feature of an antihypertensive treatment and was not misleading to prescribers.

(iii) Servier said that the claim "Trough/peak ratio of 87 - 100%" was a simple statement of fact, as it had argued in point 1, conveying the information that perindopril once daily provided consistent blood pressure control throughout the 24 hour cycle. No comparison with other ACE inhibitors was made, or implied. Servier agreed that methodological difficulties made it difficult to draw anything other than broad comparisons between agents which were clearly suitable for once daily dosing and those which were not, unless of course direct comparative methodologically accepted studies were available.

In conclusion, Servier considered that in relation to perindopril, the statement "Trough/peak ratio of 87 - 100%" accurately reflected the available literature. Servier submitted that the T:P ratio was a characteristic of an antihypertensive treatment which was relevant to prescribers in that a high T:P ratio was indicative of a consistent effect throughout the 24 hour dosing interval.

PANEL RULING

The Panel noted that the complainant referred in general to the prominent advertising of T:P ratios and discussion of these with clinicians. The only promotional material the complainant had provided was the advertisement, the subject of complaint in point 1 above. The Panel decided that in the circumstances it would limit its consideration of this allegation to the advertisement.

The Panel did not accept that the claim regarding the T:P ratio for perindopril was being used, in the advertisement in question, as a marker of clinical efficacy. No undue significance had been attached to the claim. In the Panel's view the claim informed prescribers that the T:P ratio for perindopril was such as to make the product suitable for a once daily dosage regimen. No significance was attached to the magnitude of the T:P ratio. Clinical efficacy was referred to in the claim "4mg dose controls 77% of patients". The Panel noted that the advertisement referred only to Coversyl and that there was no actual or implied comparison with other ACE inhibitors.

The Panel considered that the use of the T:P ratio in the advertisement was not misleading as alleged. No breach of Clause 7.2 was ruled.

Complaint received **8 July 1997**

Case completed **12 September 1997**

DOCTOR v PFIZER AND EISAI

Daily Mail Article on Aricept

A doctor complained about an article which appeared in the Daily Mail on 1 July 1997 which was headed "Now these pills can hold back my Alzheimer's" and which included a picture of picture of the pack for Aricept. The complainant alleged that the article was highly irresponsible and that Pfizer and its agents had for some time engaged in a deliberate campaign to promote both licensed and unlicensed medicines to the public.

Aricept was marketed in the United Kingdom by Pfizer and Eisai was the product licence holder. The matter was taken up with both companies.

The Panel noted that the author of the article had a particular interest in Alzheimer's disease and had written a book on the subject. The Panel noted that neither Pfizer nor Eisai had had any contact with the author and no information had been supplied to her by the companies. She had not been commissioned to mention Aricept. No breach of the Code was ruled.

This complaint concerned an article in the Daily Mail, 1 July 1997, regarding Aricept. Eisai Limited was the product licence holder and the product was marketed by Pfizer Limited in the UK. The matter was therefore taken up with both companies.

COMPLAINT

A doctor alleged that the article which appeared in the Daily Mail Good Health section, "Now these pills can hold back my Alzheimer's" was highly irresponsible. In a photograph which accompanied the article there was a clear picture of the Aricept pack.

The complainant understood that commercial articles for Pfizer's product Aricept (plus another named product) were placed by Pfizer's public relations agency and that the specific contact at Pfizer's public relations agency was well known to the editorial staff writers involved in the production of the Daily Mail's Good Health section.

The complainant's view was that it was quite clear that Pfizer's marketing team and its public relations agency had for some time engaged in a deliberate campaign to promote both licensed and unlicensed medicines to the public by such means with both parties being fully aware of the illegal nature of their actions.

Case AUTH/579/7/97

RESPONSE

Pfizer referred to the a response from Eisai Limited (see below).

The company also commented that the named public relations agency was engaged to promote the over-the-counter range of consumer products produced by Pfizer's subsidiary company, Unicliffe Limited (which traded under the name of Pfizer Consumer Healthcare). It had no involvement with Pfizer's prescription only medicine business and both Pfizer and the public relations agency denied the allegation that the article was placed by either party. Pfizer provided a letter from the public relations agency which stated that it was not involved in the placing of the article and that the agency was not, and never had been, employed by Pfizer to promote any of its prescription only medicines. Pfizer also denied the allegation that it was involved in a deliberate campaign with the public relations agency to promote prescription only medicines, licensed or otherwise, to the public.

Case AUTH/580/7/97

RESPONSE

Eisai submitted that the complaint was invalid and it could not reasonably be said that either Eisai or Pfizer had a case to answer.

The complainant had stated that the article was "placed" by the public relations agency which was well known to the Daily Mail journalists responsible for the "Good Health" series of features. Eisai submitted that the fundamental basis for the complaint was wrong. Eisai submitted that the public relations agency had had no communication with the author of the article in the Daily Mail or any other journalist there concerning Aricept. A letter from the author was provided which stated that she had not had any dealings with the public relations agency. If their contact was well known to the Daily Mail staff and writers this was news to her, she had no idea who the contact might be. Further, she was not commissioned to mention Aricept by the Daily Mail so she did not know where the idea that the article was somehow "placed" by Pfizer came from. The author explained that an Alzheimer's sufferer contacted her out of the blue to say she had been delighted with the difference the product had made. The author stated that the doctor running the trial described to the author how Aricept worked, taking care to mention that the product was not a cure, that it didn't work for everybody and there could be unwelcome side effects. Eisai submitted that it had no involvement with the public relations agency concerning Aricept. It had been advised by Pfizer that the public relations agency was not concerned at all with Pfizer's prescription only medicines business but only consumer products. The complaint was based either on misconceived speculation by the complainant or incorrect information provided by another.

Neither Eisai nor Pfizer had any contact with the Daily Mail concerning the article before its publication. Since the complaint Eisai had sought to establish the facts. The author had explained that it arose through an interview with the family mentioned in it concerning a patient's involvement in a clinical trial of the product. The author had also written a book on Alzheimer's disease and had a special interest in the disease. The initiative for the interview came from the journalist who composed the piece herself without any direct or indirect help or

information from Eisai or Pfizer. That such an article and many like it should be written was hardly surprising, given that Aricept represented a breakthrough in the treatment of a very serious condition - Alzheimer's disease. Aricept was the first product to be authorised in the UK for this condition.

Eisai noted that the complainant did not particularise any criticism of the substance of the article. The Code rightly controlled the delivery of information on new prescription only medicines to the public so as to ensure any legitimate news concerning new medical advances was factual and balanced so as to guard against raising unfounded hopes of successful treatment or encouraging members of the public, on the basis of misleading information, to ask their doctors to prescribe a particular product.

In the present case, Eisai suggested that the article was factual and balanced and did not raise unfounded expectations. The majority of the story was about the life of a family and the effects of Alzheimer's disease. The journalist referred to Aricept as an experimental drug (which it was at the time the trial was carried out) "which seems to help the symptoms" but the comments were responsibly moderate in tone. Indeed the article suggested the product was under research and focused on the patient's entry into a trial where it was noted: "The doctor explained that the drug was experimental, that it didn't work for everybody and that there might be side effects." The patient recorded that although she knew it could not reverse her disease, it had helped her symptoms considerably and she wished to stay on it. The story did not go into any detail about the medicine. In addition to the main article was an emboldened section in the left hand corner which recited comments of a named doctor (who Eisai now understood was the investigator in the trial in which the patient was enrolled). The company had no contact with the doctor and her involvement was also entirely unconnected with Eisai or Pfizer. The journalist contacted the doctor independently and the comments were objective, balanced and restrained. She explained in simple language what Aricept did and its limitations. She noted: "It doesn't work for everybody and patients won't get back the memory already lost ... We are concerned that the patient must be correctly diagnosed before it is prescribed ... Aricept is suitable only for mild to moderate Alzheimer's - not for the very serious stages." The pack shot which appeared with the article seemed to be of the clinical trial pack for donepezil and neither Eisai nor Pfizer had provided it. Eisai assumed that it came from the patient or clinician featured.

Eisai commented upon the article itself because the complaint raised an important point of principle which the Panel needed to address in the new environment of increased patient awareness and interest in health issues. The lay media was increasingly publishing a great deal of material on health, treatment of disease and new medicines in general. This reflected the public's increasing thirst for information in the field. This was therefore a "growth area" and it could not be right that every time an article arose referring to a new drug (whatever its contents and however flawed the supposition on which any complaint was based) the licence holder or distributor should be required to involve itself in the collation and examination of any information it has made available to the media. If a piece was clearly unbalanced and offended against the principles of the Code, then a legitimate question arose as to why that might be and it was perfectly reasonable to ask that the companies connected with the product mentioned provided press materials so that their possible responsibility could be assessed. Companies did provide information to the lay press and, if there was a *prima facie* case that these materials were the cause of unbalanced reporting, the Panel should not be slow to investigate their possible involvement. However, there must be a threshold that triggered such an investigation and Eisai believed that an ill-founded allegation that an article was "placed" should not be sufficient.

Eisai submitted that it felt particularly strongly about this because the launch of Aricept unquestionably represented a scientific advance and because the launch of its European business was inextricably linked to the research and marketing of Aricept. It had, therefore, had press conferences and issued press releases coinciding with the establishment of its business and the opening of its offices by the then Minister of Health (which was accompanied by a presentation on Alzheimer's disease by a distinguished academic) and the licensing of Aricept by the authorities in the USA and UK. Eisai could collate the information and materials that had been presented to the medical and lay press but believed that this should not be required unless and until it was shown that there was a case to answer in that there was some evidence that the information supplied might have been the basis for unbalanced reporting.

Eisai pointed out that it had been confirmed by the author that she did not have access to press information or materials produced by Eisai or Pfizer. The author was a freelance journalist and as such she did not receive any press information or materials made available to the Daily Mail.

Only where links were established which connected particular companies with unbalanced press articles and which, therefore, suggested that a breach of the Code might have been committed should the involvement of companies be examined. In this case Eisai respectfully suggested that it had provided clear evidence from the journalist herself that neither Eisai, Pfizer nor the public relations agency had any involvement in the preparation of the Daily Mail article in question.

Eisai believed that it could reasonably ask the Panel to rule that there was no case to answer.

CASES AUTH/579/7/97 and AUTH/580/7/97

PANEL RULING

The Panel noted Eisai's general comments regarding complaints about articles in the media etc and whether such articles should be assessed prior to initiating the complaints procedure. The Panel noted that Eisai was in effect asking for a ruling prior to obtaining the respondent company's comments on the matter. Further, the Panel noted the submission from Eisai that an ill founded allegation should not be sufficient to trigger the complaints procedure. However, when a complaint was received it was not usually possible to assess whether or

not it was ill founded. This did not generally happen until the response had been received from the company concerned. The Authority was obliged to follow its Constitution and Procedure.

The Panel noted that complaints about articles in the media etc were judged on the material provided and not on the content of the article itself. Following receipt of a complaint the Director was obliged by Paragraph 5.1 of the Constitution and Procedure to ask for comment on the complaint.

The Panel noted that the author of the article had a particular interest in Alzheimer's disease. She had written a book on the subject. The article referred to Alzheimer's Awareness Week which was to run the week following the publication of the article. The name and address of the Alzheimer's Disease Society were given.

The Panel noted that the neither Pfizer nor Eisai had had any contact with the author of the article. No information had been supplied by the companies to the author and the author had not been commissioned by the Daily Mail to mention Aricept.

The Panel decided that as neither company had had any contact with the author, there could be no breach of the Code and ruled accordingly.

Complaint received **11 July 1997**

Case completed **8 September 1997**

CASE AUTH/582/7/97

COMMUNITY PHARMACIST v SCHERING-PLOUGH

Supply of Cedax

A community pharmacist complained that he had taken stock of Cedax Suspension from a representative of Key Pharmaceuticals on a sale or return basis but when he tried to return it he had been unable to obtain a satisfactory response from either the representative or the company itself.

The Panel considered that the company had failed to honour an agreement made in the course of promotion. The representative alone was not to blame as the complainant had approached the company's head office on a number of occasions. High standards had not been maintained and the Panel ruled that there had been a breach of the Code.

A community pharmacist submitted a complaint about the promotion of Cedax Suspension by Key Pharmaceuticals, part of Schering-Plough Ltd.

COMPLAINT

The complainant explained that last year a representative of Key Pharmaceuticals called to assist in a promotion of Cedax Suspension. The pharmacy agreed to have a sale or return supply which the representative left with the pharmacy together with his business card and a telephone number.

The complainant said there was no demand for the product which in due course became out of date. He telephoned the number left with the business card but this proved to be unobtainable. He subsequently telephoned Key Pharmaceuticals to explain the matter and seek assistance. Despite several calls, there was no response. On 20 December 1996 he wrote to Key Pharmaceuticals explaining there had been no demand for Cedax to date and now he wanted to return it for exchange. The letter explained that he had been unable to contact the representative to call to resolve this outstanding matter. Following the letter Key Pharmaceuticals had contacted the pharmacy seeking a full set of information and promising to send a representative to deal with the matter. Nothing happened and the complainant wrote again on 21 March 1997 stating that the failure to respond to the now long-standing letter was astounding and when could he have some action on the matter. No response had been received.

The complainant said that the pharmacy was pleased to co-operate with manufacturers in promoting new products but on this occasion it had been badly let down in the standard expected from a reputable company.

RESPONSE

Schering-Plough Ltd explained that the representative concerned was seconded from his territory to head office in Welwyn Garden City from May to December. This explained why the telephone number left with the complainant was unobtainable.

The company believed it was the representative himself who contacted the pharmacy shortly after the letter of 20 December 1996. The representative agreed to visit the pharmacy in the new year when he returned to his territory. In the second week of January 1997, the representative was appointed permenantly to head office after an unexpected vacancy. This required an immediate move back to Welwyn Garden City. A replacement representative was not appointed immediately. The details of the complainant's situation regretfully were not attended to.

The company said it was keen to put matters straight with the complainant and would have no hesitation in crediting him with alternative stock. The representative had been reprimanded and reminded of his commitment to customer service.

PANEL RULING

The Panel noted that this case arose from a visit by the representative to the pharmacy whereby the pharmacist was given a supply of Cedax on a sale or return basis.

Despite several approaches from the pharmacist by both telephone and post, the pharmacist had failed to receive a response from Schering-Plough.

The Panel noted that the representative had promoted Cedax on a sale or return basis. The complainant had been given stock but had not been able to return it. The company's silence on the matter over a course of several months could be seen to amount to refusal. The Panel acknowledged that it was difficult to know where promotional offers ended and office procedures began but considered that in this case the company had failed to honour a specific agreement made in the course of a particular promotion. The Panel did not accept that the representative alone was to blame as the complainant had approached head office on a number of occasions. The Panel considered that the company had failed to maintain a high standard of ethical conduct and therefore ruled a breach of Clause 9.1 of the Code.

Complaint received **14 July 1997**

Case completed **13 August 1997**

CASE AUTH/584/7/97

HOSPITAL PHARMACIST v NOVARTIS

Lescol advertisement

A hospital pharmacist complained about an advertisement for Lescol issued by Novartis which featured a picture of a chocolate eclair. It was alleged that the picture could be interpreted as meaning that diet was unimportant when Lescol was prescribed but its prescribing information stated "place patient on a standard cholesterol lowering diet, which should be continued during treatment".

The Panel considered that the impression given was that there was no need to worry about diet when prescribing Lescol and this was misleading. In the Panel's view, the advertisement did not make it sufficiently clear that patients should continue on a standard cholesterol lowering diet. A breach was ruled.

A hospital pharmacist submitted a complaint about an advertisement for Lescol issued by Novartis Pharmaceuticals UK Ltd. The advertisement appeared in the British Medical Journal, 5 July 1997. It was headed "Are you squeezing enough from your statin?" beneath which appeared a photograph of a chocolate eclair. Underneath the photograph was the statement "When diet has failed" followed by the product name, Lescol, followed by the statement "Keeping lipid levels down against the pound".

COMPLAINT

The complainant said that although it could be argued that the advertisement was "tongue-in-cheek", the picture of the chocolate eclair could be interpreted as meaning that diet was unimportant if Lescol was prescribed in a patient with hypercholesterolaemia. The complainant alleged that if this was so, the advertisement was misleading as the dosage section of the prescribing information stated "place patient on a standard cholesterol lowering diet, which should be continued during treatment".

RESPONSE

Novartis pointed out that Lescol was indicated for the management of hypercholesterolaemia in patients with cholesterol levels in excess of 6.5mm/l, who had not responded to dietary therapy alone. The need for concomitant dietary control was a recognised element with all statin therapy and with this clearly in mind, all advertisements for Lescol deliberately and prominently included a statement that the product should be used only when diet had failed. It was not the company's intention to suggest in any way that the dietary element of the patient's care was unimportant as suggested by the complainant. A statement about dietary control also appeared in both the "Indications" and the "Dosage and Administration" sections of the prescribing information.

Novartis accepted that the photograph of the eclair was slightly "tongue-in-cheek", the company submitted that Clause 9.1 of the Code did not preclude all forms of gentle humour in promotional materials and did not consider that the image in any way disregarded the professional standing of the audience. The statement "when diet has failed" was added to ensure that the gentle humour of the image did not detract from the serious nature of the therapeutic message. It was important to note that the photograph of the eclair was chosen to convey a visual analogy for a vessel filled with a fatty substance, in this case cream representing cholesterol and that Lescol would assist the prescriber to squeeze more fat from the vessels, when diet alone had failed.

Novartis submitted that the association between squeezing the fat from an eclair with the idea of eliminating fat from blood vessels with Lescol gave a striking image which had been generally well received by prescribers.

PANEL RULING

The Panel noted that the prescribing information stated that patients should be placed on a standard cholesterol lowering diet which should be continued during treatment with Lescol. The Panel considered, however, that the impression of the advertisement was that there was no need to worry about diet when prescribing Lescol and this was misleading. The text could be read to mean that subsequent to a failed diet Lescol could be prescribed as an alternative, as opposed to an additional, method of lowering cholesterol. In the Panel's view the main body of the advertisement did not make it sufficiently clear that patients should continue on a standard cholesterol

lowering diet during treatment with Lescol. The Panel therefore ruled a breach of Clause 7.2 of the Code.

Complaint received	**16 July 1997**
Case completed	**20 August 1997**

CASE AUTH/585/7/97 *NO BREACH OF THE CODE*

RESEARCH ETHICS COMMITTEE v PARKE-DAVIS

Atorvastatin study

A local research ethics committee complained about a study on atorvastatin to be carried out on behalf of Parke-Davis. The ethics committee was not convinced that the study was necessary as there were already two well established medicines on the market. Atorvastatin was already a licensed medicine and as patients would continue on it after the trial, the committee considered the study to be purely a marketing exercise.

The Panel observed that the only relevant provision in the Code was the requirement that such studies must not be disguised promotion. Any study would inevitably have some promotional impact. The Panel noted that the primary aim of the study was to assess the efficacy of a dosage regime which started all patients at the recommended dose of 10mg and then, based on the response, titrated straight to a tailored dose to achieve target lipid lowering goals as defined by the British Hyperlipademia Association. The secondary objective was to assess the efficacy of atorvastatin in lowering lipid levels compared to baseline.

The Panel had a number of comments on the detail of the protocol but did not consider that the study was promotional in nature. The payments to be made to participating doctors were reasonable. The Panel ruled that there had been no breach of the Code.

A local research ethics committee submitted a complaint about a study on atorvastatin in general practice to be carried out on behalf of Parke Davis & Co Limited. The study was an open, non-comparative multicentre study in patients with existing CHD and dyslipidaemia. The primary aim of the study was to assess the efficacy of a dosing regimen starting all patients at the recommended dose of 10mg and then, based on their response, titrating to a tailored dose to achieve target lipid lowering goals as defined by the British Hyperlipidaemia Association. Patients recruited into the trial received a patient information sheet.

COMPLAINT

The director of public health at a health authority stated that the local research ethics committee had discussed the protocol in some depth and decided not to give ethical approval to proceed. The ethics committee was not convinced that the study was necessary as there were already two established medicines backed by numerous trials currently on the market. Atorvastatin was already a licensed medicine and as patients would continue on the medicine at the end of the trial it was considered that the protocol was purely a marketing exercise. The ethics committee commented that if it was in fact shown that the medicine was as effective at the lower dose as at the higher dose, it would corner the market as its price was so low. The patient information sheet should also include that alternative therapy had been shown to improve survival. Following discussion it was agreed that before ethical approval was given, advice be sought from the ABPI as to its views on the justification of the trial taking place if purely a marketing exercise. The ethics committee had had a response from the medical director of the ABPI who said that if the committee considered the trial was a seeding trial, it was in order for it to complain to the Authority and the complaint would be that in promoting this trial Parke-Davis was not adhering to Clause 10.2 of the Code which required that market research activities, post-marketing surveillance studies, clinical assessments and the like must not be disguised promotion.

RESPONSE

Parke-Davis strongly contested any allegation that the study lacked scientific merit and was merely a form of "disguised promotion". It did not accept that the study was in breach of Clause 10.2 of the Code. Parke-Davis pointed out that 32 ethics committees had approved the study in 49 sites to date. It was also awaiting written approval from a further three committees to give the company another five sites. Currently 140 patients had been recruited into the study.

The company submitted that the design of the study was scientifically rigorous and well suited to achieve the study objectives and that the study objectives were appropriate as the study might lead to important information which might influence the future management of high risk hypercholesterolaemic patients in general practice.

Much deliberation took place during the design and development of the study which started late last year under the auspices of a steering committee comprising of Parke-Davis and Pfizer clinical trials and medical personnel and the independent advisors; a professor of general practice and a university lecturer in clinical epidemiology. In the planning, consideration was given to the fact that the patients would not actively present and could be difficult to identify, except by the active audit of patient records. With this in mind and advice from the steering committee it was decided that it would be necessary for the study to be a multicentre study involving approximately 65 centres with each centre recruiting about six patients.

To summarise: the study had a protocol, involved a comprehensive series of laboratory tests which were sent to a central laboratory, all doctors must complete case report forms, doctors must also monitor adverse events, statistical data analysis would be performed, local ethics committee approval must be obtained and the study must

comply with GCP provisions which included the storage of all documentation for 15 years. In addition, the company intended to publish the results of the study and study payments were in line with the suggested charging rate by the British Medical Association.

Parke-Davis pointed out that the summary of product characteristics (SPC) for atorvastatin showed that the usual starting dose was 10mg once a day. It was estimated that at least 60% of patients would achieve their LDL-cholesterol target levels at this dose and 85% would achieve target overall. The study was adequately powered to estimate the proportion of patients achieving target cholesterol levels. Those remaining patients who did not achieve British Hyperlipidaemia Association (BHA) target levels after four weeks of therapy with the 10mg daily starting dose of atorvastatin would have their dose increased directly to 20, 40 or 80mg of atorvastatin depending on their LDL-cholesterol level. This was clearly described in the statistical section of the protocol for the study.

The primary aim of the study was to assess the efficacy of a dosing regime starting all patients at the recommended dose of atorvastatin 10mg daily and then, based on the patient's response, increasing the dose to achieve target cholesterol levels as defined by the BHA. The secondary objective was to assess the efficacy of atorvastatin in lowering lipid levels compared to baseline.

Parke-Davis submitted that whilst previous studies had proven that atorvastatin was an effective agent for lowering cholesterol in patients with hyperlipidaemia this general practice study was innovative in two respects. Firstly drug therapy initiation was based on the BHA guidelines, and secondly it used a novel two-step dosage titration.

This was the very first trial that Parke-Davis had undertaken using the BHA guidelines, rather than either the American NCEP or European Atherosclerosis Society Guidelines. This was a study in general practice which would encompass a much wider, more diverse patient population than that allowed by the strict criteria used in controlled trials in specialist hospital centres. Moreover, because of the general practitioner's unique relationship with the patient and familiarity with their medical history and concomitant therapy, he/she was best placed to assess patient compliance and the effectiveness of the dosing regimen. Indeed, this was endorsed by the British Medical Association, the Royal College of General Practitioners and the ABPI, which had jointly agreed the Code of Practice for the Clinical Assessment of Licensed Medicinal Products in General Practice (1992).

The study would provide valuable data regarding how well general practitioners accepted the two-step dose titration approach to patient management. The company knew that the traditional multiple visit approach was inconvenient for both the patient and the doctor where this involved several patient assessments by the GP, multiple prescriptions and a general increased workload for the doctor. With the simplified dosing regime in the study, all patients started at 10mg/day atorvastatin to ensure that patients who responded to 10mg once daily and achieved their target levels would not be treated with unnecessarily high dose drug therapy. However, for those patients that did not achieve their target levels at 10mg/day, the general practitioner could increase the dose directly to either 20, 40 or 80mg daily according to their LDL-cholesterol level. If this approach was successful it would demonstrate that the two-step approach to lipid lowering was a realistic strategy for treating patients in primary care.

The company submitted that relatively few general practitioners treated their patients with existing heart disease (myocardial infarction, post-CABG, angioplasty) and dyslipidaemia (LDL-cholesterol > 3.4mmol/l and triglycerides < 5.5mmol/l). Moreover, several studies had reported that appropriate drug therapy was not implemented in routine clinical practice. A recent practice audit by Dr Andrew Pilbeam, published in General Practitioner on 10 January 1997, showed that only 18% of patients after a myocardial infarction were on lipid lowering therapy. In a follow up study of a cohort of myocardial infarction survivors in the Oxfordshire area, Dovey *et al* were able to show that appropriate hospital initiated prescribing could achieve higher rates of adherence to drug therapies for secondary prevention of myocardial infarction than previously reported. The company envisaged that a publication from the study would be used to educate and inform general practitioners throughout the country about the ease of using lipid lowering therapy in primary care to lower cholesterol levels according to the BHA guidelines.

To reiterate the important points, the company believed that the study was medically robust, had scientific merit and was, in fact, important to the future management of high risk patients. Clinically, the study did have an important purpose and that purpose was to assess the efficacy of a novel dosing regime starting all patients at the recommended dose of atorvastatin 10mg daily and then, based on the patient's response, directly adjusting the dose to achieve target lipid lowering goals as defined by the BHA. This approach to drug intervention therapy had not previously been studied in general practice.

With respect to the other comments made by the complainant, the company accepted that patients at the end of the study might continue on their study drug. However, this decision rested solely with the treating doctor; there was no requirement for them to do so. The company did not understand the specific comment made by the research ethics committee about the lower dose being as effective as the higher dose and how this would corner the market on price. The aim of the study was to determine the effect of atorvastatin using a simplified two-step regimen instead of a possible four-step regimen on lowering cholesterol. After an initial five weeks of therapy with atorvastatin 10mg daily the dose was adjusted according to the patient's LDL-cholesterol level (at visit 3) to either atorvastatin 20, 40 or 80mg daily if target cholesterol levels were not achieved. The study did not aim to show that 10mg was as effective as higher doses - the company knew already from dose-ranging studies that it was not. The company failed to see the relevance of the research ethics committee's statement on Lipitor's price and its success in the market place.

With regard to the patient information sheet, the company could certainly make appropriate amendments to the text. This sheet was, of course, based on the current Medicines Control Agency approved patient information leaflet (and on guidelines for information leaflets for patients taking

part in clinical trials), but the company welcomed constructive ideas on ways to improve the nature and understanding of the information provided on its medicines to patients. The process, however, required a dialogue which, so far, had not been possible. The company was confused by the research ethics committee's final sentence which suggested that it did agree to seek advice from the ABPI as to its view on the justification of this trial. The company noted that the ABPI's medical director was contacted and that he had suggested that the committee refer the matter to the Authority as a formal complaint if it considered the study to be a "seeding" trial. The company had not been made aware of any discussion that the ABPI and the research ethics committee had had regarding the matter.

The company was disappointed that this matter had been treated as a formal complaint by the Authority on first hearing of it from the local research ethics committee. The company had not received any correspondence from any research ethics committee relating to this matter and, as in a previous case, the company believed that it could have avoided a formal complaint by being given the opportunity of directly addressing the concerns that the local research ethics committee had with this study. The company believed that the initial enquiry to the ABPI was purely for comment with the aim of confirming or refuting the fact that the study was or was not purely for promotional purposes to market the drug. Clearly, local ethics committees were unaware that the ABPI/Authority could not advise on such matters unless a formal complaint was submitted. A more pragmatic approach should be introduced to deal with such an enquiry which would satisfy both ethics committees and industry needs.

PANEL RULING

The Panel noted Parke-Davis' comments about the Authority's decision to deal with the matter as a formal complaint. The Authority's view had been that the research ethics committee had approached the ABPI for advice and on the basis of the advice received had decided to submit a complaint to the Authority. There was nothing to prevent the ABPI from giving what advice it saw fit about a study.

The Panel noted that the only clause in the Code relating to clinical trials and the like was Clause 10.2 which required that studies must not be disguised promotion. Any study would inevitably have some promotional impact.

The Panel examined the study protocol. The primary aim of the study was to assess the efficacy of a dosing regime starting all patients at the recommended dose of 10mg and then, based on the response, titrate straight to a tailored dose to achieve target lipid lowering goals as defined by the BHA. The secondary objective was to assess the efficacy of atorvastatin in lowering lipid levels compared to baseline.

The Panel noted that approximately 65 centres throughout the UK and Eire would recruit 400 patients. Each general practitioner was asked to recruit a minimum of six patients. The medication would be delivered to and dispensed by the general practitioner. The treatment plan was such that patients followed a diet for a period of five weeks following which, if the patient qualified for lipid lowering medication, the patient would be dispensed 10mg atorvastatin for a five week period. Following this a fasting blood sample would be taken. The LDL-C level would determine the dose of atorvastatin (10, 20, 40 or 80mg) to be used for the remainder of the study (12 weeks). The final visit, visit four, occurred at week 22 of the study. The protocol stated that doctors should thank patients for participating in the study and "manage appropriately".

The introduction to the study stated that it had been designed to investigate, in a general practice setting, the ability of atorvastatin to meet the lipid lowering goal set out in the BHA Guidelines. The protocol stated that "The Health of the Nation" policy document (June 1992) outlined a target CHD reduction of 30% expected in the UK by the year 2000. In contributing to this 30% reduction physicians were required to treat abnormal lipids more actively to reach target LDL-C levels. The protocol stated that dietary advice was the first line of attack in any patient with hyperlipidaemia. The introduction to the study referred to the BHA Guidelines and stated that the first priority for treatment should be patients with existing CHD or post CABG, angioplasty or cardiac transplant. The aim of drug treatment in such patients should be to lower LDL-C to less than 3.4mmol/L. In this context a placebo control study would not be ethical. It also stated that atorvastatin presented itself as a suitable candidate for such therapy as it had been shown to be highly effective in lowering lipid levels.

The Panel made a number of comments about the study. It was an open non-comparative study and an active comparator might have been helpful although this might have caused problems with blinding the study. As far as the Panel could see, patients for inclusion had to have existing coronary heart disease (myocardial infarction, CABG, angioplasty) and dyslipidaemia. No mention was made of taking controlled patients off existing medication. At the completion of the trial no comment was made as to the post-trial medication other than that following the last visit patients should be managed appropriately. The Panel also noted that Lipitor was indicated as an adjunct to diet. At the beginning of the study patients had to follow a diet prior to taking any medication. The SPC for Lipitor stated that patients should continue on a standard cholesterol lowering diet during treatment. In the Panel's view the documentation gave the impression that diet was to be followed prior to taking the medication. It was not made clear whether or not diet was to continue following the introduction of atorvastatin. The Panel assumed that as the study was within the product licence, standard cholesterol lowering diet would continue throughout the study.

The Panel noted that patients enrolled into the study were to make four visits to the investigator. In addition one week prior to visit two, and one week prior to visit three, fasted 15ml blood samples for lipid and safety analyses had to be collected. The Panel noted that the payment for each evaluable patient was £350. The Panel considered that the payments were reasonable given that the British Medical Association suggested fees for participation in clinical trials was, according to the Authority's information, £126 per hour and pro-rata.

The Panel did not consider that the complainant's comments regarding the fact that, if it was shown that

atorvastatin was as effective at the lower dose as at the higher dose it would corner the market as its price was so low, or that there were already two established medicines backed by numerous trials currently on the market, were relevant as far as the Code was concerned.

The Panel considered that the study was not promotional in nature and therefore no breach of the Code was ruled.

Complaint received 16 July 1997

Case completed 29 September 1997

CASE AUTH/592/8/97

SERONO v FERRING

Menogon brochure at international meeting

Serono complained about a brochure for Menogon which had been distributed by Ferring at an international meeting held in Edinburgh. It was alleged that it failed to state that Menogon did not have a marketing authorization in the UK.

The Panel noted that the supplementary information to the Code permitted promotional material for products which did not have a marketing authorization in the UK, but were so authorized elsewhere, to be used at truly international meetings in the UK provided that certain conditions were met including a need to clearly indicate on the material that the product did not have a UK marketing authorization. The brochure did not include any statement about the licensing status of Menogon in the UK and the Panel ruled that the brochure was in breach of the Code.

Serono Laboratories (UK) Ltd complained about a product information brochure for Menogon which was distributed by Ferring Pharmaceuticals Limited at the European Society of Human Reproductive Endocrinology (ESHRE) meeting which took place in Edinburgh from 22 to 25 June 1997. The brochure was provided to health professionals who attended the Ferring stand.

Ferring was not a member of the ABPI but had nevertheless agreed to comply with the Code.

COMPLAINT

Serono alleged that the brochure was in breach of Clause 3.1 of the Code as it constituted promotion for Menogon which did not have a marketing authorization in the United Kingdom.

Serono noted that the supplementary information to Clause 3 of the Code permitted the promotion of medicines which did not have a marketing authorization in the UK at international conferences held in the UK. Such material had to clearly state that the medicine was not authorized for use in the UK. No such statement was included in the Menogon brochure.

Serono alleged that the brochure contravened the EC Directive on the advertising of medicinal products for human use.

RESPONSE

Ferring confirmed that the brochure had been distributed at the ESHRE meeting in Edinburgh and provided the Panel with a leaflet about the ESHRE meeting to confirm its international status.

Ferring stated that Menogon did not have a UK marketing authorization. An application for authorization had been submitted and the product was in the final stages of the process. Ferring pointed out that Menogon did have a marketing authorization in Germany and in the Netherlands.

Ferring conceded that the Menogon brochure did not carry any clear indication that the product was not the subject of a marketing authorization in the UK.

Ferring submitted that it had been vigilant to the requirements of Clause 3 of the Code regarding the promotion of medicines without a marketing authorization at international meetings and had drawn the requirements of Clause 3 of the Code to the attention of its corporate international marketing colleagues who were coordinating Ferring's attendance at the ESHRE meeting. Ferring provided the Panel with a copy of a facsimile dated 20 May 1997 which it had sent to its colleagues regarding the promotion of products which did not have a marketing authorization in the UK at the ESHRE meeting. The facsimile stated that the representatives of Ferring at the exhibition stand "....must not be seen to be promoting to customers from countries where a product is not available. Could you please ensure that all concerned are aware that UK doctors must not be detailed!".

Ferring regretted the incident which overstepped its guidelines. It would bring the matter to the urgent attention of its corporate colleagues.

PANEL RULING

The Panel noted that Serono had alleged a breach of the EC Directive on the advertising of medicinal products for human use. The Panel was only able to rule in relation to the requirements of the Code. The Code did of course reflect the requirements of the EC Directive.

The Panel noted that international meetings held in the UK were subject to the UK Code of Practice. Companies operating in the UK were responsible under the Code for activities in the UK of their overseas parents and affiliates. Ferring UK was therefore responsible for the activities of its corporate international marketing colleagues.

The Panel considered that the brochure was promotional for Menogon. The Panel noted that Menogon did not have a UK marketing authorization although it was so authorized in Germany and the Netherlands.

The Panel examined the requirements of Clause 3 of the

Code together with the supplementary information headed "Promotion at international conferences". The supplementary information stated that the display and provision of promotional material for medicines which did not have a marketing authorization in the UK, although they were so authorized elsewhere, was permitted at international meetings in the UK provided that any promotional material for medicines or for indications which did not have a UK marketing authorization were clearly and prominently labelled as such. The meeting had to be a truly international meeting of high scientific standing with a significant proportion of delegates from outside the UK and the promotional material had to be certified.

The Panel noted that the Menogon brochure did not contain any statement about the licensing status of Menogon in the UK and had thus failed to meet one of the conditions in the supplementary information. The brochure was therefore ruled to be in breach of Clause 3.1 of the Code.

Complaint received **1 August 1997**

Case completed **18 September 1997**

CASE AUTH/596/8/97 *NO BREACH OF THE CODE*

CONSULTANT PHYSICIAN v RECKITT & COLMAN

Promotion of Gaviscon Advance

A consultant physician complained about a mailing consisting of a letter and a leaflet sent by Reckitt & Colman about the launch of Gaviscon Advance. The complainant noted that Gaviscon Advance contained twice as much alginate as Gaviscon but half the quantity of antacid and cost twice as much per unit volume. It cost no more per dose of alginate but twice as much per unit of antacid. The complainant alleged that the claim for Gaviscon Advance that it "costs no more to prescribe per dose" was misleading. The complainant furthermore suspected that the same volume of Gaviscon Advance would be expected by the patient, and therefore prescribed by the doctor, as was traditional with Gaviscon. He doubted that prescribing costs would fall.

The Panel noted that Liquid Gaviscon and Gaviscon Advance were both licensed with the same indications and that Gaviscon Advance was to be used at half the dose of Liquid Gaviscon. The Panel noted that there was no difference in the cost per dose at either the lower dose or the higher dose of each product. The Panel noted that neither the letter nor the leaflet had indicated that costs would fall with the use of Gaviscon Advance, only that the product would cost no more per dose than Liquid Gaviscon. In the Panel's view, Reckitt & Colman was not responsible if the same volume of Gaviscon Advance was prescribed as for Gaviscon Liquid. Both the letter and the leaflet referred to the reduced volume needed to treat with Gaviscon Advance.

The Panel did not accept that the material was misleading and no breach of the Code was ruled.

A consultant physician complained about a mailing from Reckitt & Colman Products Limited which informed recipients of the launch of Gaviscon Advance. Reckitt & Colman although not a member of the ABPI had nevertheless agreed to comply with the Code. The mailing consisted of a letter and a leaflet. Gaviscon Advance was referred to in the mailing as a new improved formulation of Gaviscon Liquid.

COMPLAINT

The complaint was about a claim for Gaviscon Advance that it "costs no more to prescribe per dose".

The complainant noted that Gaviscon Advance contained twice as much alginate as Gaviscon (500mg versus 250mg per 5ml) but half the quantity of antacid (100mg vs 214mg per 5ml) and cost twice as much per unit volume. It therefore cost no more per dose of alginate, but twice as much per unit of antacid. The complainant knew of no reason to suppose that the efficacy of alginate/antacid combinations was dependent entirely on the amount of alginate, and suspected that in many instances it would depend (or be perceived to depend) on the total volume administered.

The complainant alleged that the claim was therefore misleading and, in practice, he suspected that the same volume of Gaviscon Advance would be expected by the patient, and therefore prescribed by the doctor, as was traditional with Gaviscon. The complainant doubted that prescribing costs would fall and Reckitt & Colman offered no evidence that they did. He thought that the claim should be withdrawn and a correction issued.

RESPONSE

Reckitt & Colman's justification for considering that its claim that, compared with Liquid Gaviscon, Gaviscon Advance "costs no more to prescribe per dose" was correct was as follows:

i) Both Liquid Gaviscon and Gaviscon Advance were licensed for the same indications - ie gastric reflux, reflux oesophagitis, heartburn, hiatus hernia, flatulence associated with gastric reflux, heartburn of pregnancy, all cases of epigastric and retrosternal distress where the underlying cause was gastric reflux.

ii) The licensed dosage for Liquid Gaviscon was 10 - 20ml. The licensed dosage for Gaviscon Advance was 5 - 10ml.

iii) The cost of a 500ml bottle of Liquid Gaviscon was £2.70 for 50 to 25 doses, depending upon the regimen used. The cost of 500ml of Gaviscon Advance was £5.40 for 100 to 50 doses, depending upon the regimen used.

iv) In each case the cost per dose of these two products was identical at 5.4p or 10.8p, depending upon the

regimen used.

Reckitt & Colman noted that the supplementary information to Clause 7.2 of the Code headed "price comparisons" stated that to ensure that price comparisons were accurate, fair and not misleading they must be "made on the basis of the equivalent dosage requirement for the same indications".

Reckitt & Colman said that the complainant referred to the different volumes of alginate and antacid in the two products. This was irrelevant to the comparative statement. As already mentioned both products were licensed for the same indications, following the company's production of data to the UK licensing authority that they were efficacious for those indications at the stated dosage levels.

Reckitt & Colman submitted that it had followed the guidance closely and considered that the claim was correct and capable of substantiation.

Reckitt & Colman noted that the complainant also questioned whether prescribing costs would fall as a result of the availability of Gaviscon Advance for conditions previously treated by Liquid Gaviscon. In response to this the company made two points:

i) The material did not state, or indeed infer, that the availability of Gaviscon Advance would reduce prescribing costs.

ii) The assumption must always be made that doctors would read, understand and follow the dosage instructions on medicines. It was not possible to licence or sell medicines on any other basis. The dosage instructions for the two products were quite explicit. The lower dosage of Gaviscon Advance to that of Liquid Gaviscon was clearly stated on the label and leaflet and emphasised in all promotional material as one of the key benefits of the new product. The company thought it highly unlikely that doctors would prescribe the same volume of Gaviscon Advance as of Liquid Gaviscon purely to meet the patients' expectations. Reckitt & Colman noted that the complainant provided no data with which to support his hypothesis.

Reckitt & Colman said that GPs had a professional and ethical duty to ensure that their patients were given the appropriate medication, at the appropriate dosage level, to meet their therapeutic needs. If the complainant considered that he had adequate data to show that his colleagues did not operate to these criteria then this was a situation which extended beyond the prescribing of Gaviscon products to all medicines and should be taken up with the royal colleges and the Medicines Control Agency.

PANEL RULING

The Panel noted that Liquid Gaviscon and Gaviscon Advance were licensed for the same indications. Gaviscon Advance was to be used at a lower dose (5 -10ml four times daily) than Liquid Gaviscon (10 - 20ml four times daily). The Panel noted that there was no difference in the cost per dose of treating the indications at either the lower dose of each product or the higher dose of each product. The Panel noted that neither the letter nor the leaflet had indicated that costs would fall with the use of Gaviscon Advance, only that the product would cost no more per dose than Liquid Gaviscon.

The Panel accepted that the constituents of a dose of Gaviscon Advance would be different to a dose of Liquid Gaviscon as noted by the complainant. The proportions of alignate and antacid differed.

In the Panel's view Reckitt & Colman was not responsible if the same volume of Gaviscon Advance was given to patients as was recommended for Gaviscon Liquid provided that Reckitt & Colman when promoting Gaviscon Advance had given clear dosage instructions. Both the letter and the leaflet referred to the reduced volume needed to treat with Gaviscon Advance.

The Panel did not accept that the material was misleading and no breach of the Code was ruled.

Complaint received **5 August 1997**

Case completed **29 September 1997**

CODE OF PRACTICE REVIEW - NOVEMBER 1997

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

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PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

The Prescription Medicines Code of Practice Authority was established by The Association of the British Pharmaceutical Industry (ABPI) in 1993 to operate the Code of Practice for the Pharmaceutical Industry at arm's length from the ABPI itself.

Compliance with the Code is obligatory for ABPI member companies and, in addition, more than fifty non member companies have voluntarily agreed to comply with the Code and to accept the jurisdiction of the Authority.

The Code covers the advertising of medicines to health professionals and administrative staff and also covers information about such medicines made available to the general public.

It covers:

- journal and direct mail advertising
- the activities of representatives including detail aids and other printed material used by representatives
- the supply of samples
- the provision of inducements to prescribe, supply or buy medicines by the gift, offer or promise of any benefit or bonus, whether in money or in kind
- the provision of hospitality
- the organisation of promotional meetings
- the sponsorship of scientific and other meetings including payment of travelling and accommodation expenses in connection therewith
- the provision of information to the general public either directly or indirectly
- all other sales promotion in whatever form, such as participation in exhibitions, the use of audio-cassettes, films, records, tapes, video recordings, electronic media, interactive data systems, the internet and the like.

Complaints submitted under the Code are considered by the Code of Practice Panel which consists of the three members of the Code of Practice Authority acting with the assistance of independent expert advisers where appropriate. Both complainants and respondents may appeal to the Code of Practice Appeal Board against rulings made by the Panel. The Code of Practice Appeal Board is chaired by an independent legally qualified Chairman, Mr Philip Cox QC, and includes independent members from outside the industry.

In each case where a breach of the Code is ruled, the company concerned must give an undertaking that the practice in question has ceased forthwith and that all possible steps have been taken to avoid a similar breach in the future. An undertaking must be accompanied by details of the action taken to implement the ruling. Additional sanctions are imposed in serious cases.

Complaints about the promotion of medicines should be sent to the Director of the Prescription Medicines Code of Practice Authority, 12 Whitehall, London SW1A 2DY (telephone 0171-930 9677 facsimile 0171-930 4554).