PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

NUMBER 11 FEBRUARY 1996

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.

New Code of Practice and Constitution and Procedure

The 1996 edition of the Code of Practice for the Pharmaceutical Industry together with the revised Constitution and Procedure for the Prescription Medicines Code of Practice Authority was published at the beginning of the year.

Details of the changes were sent to companies towards the end of last year. They were invited to state how many copies of the new Code they required and those requests have been met. Anyone wishing to have further copies should contact Emer O'Reilly at the PMCPA (0171-930 9677 extn 1443).

The new Code of Practice came into operation on 1 January 1996 but during the period 1 January 1996 to 31 March 1996 no promotional material or activity will be regarded as being in breach of the Code if it fails to comply with its provisions only because of requirements which the 1996 edition newly introduces.

The revised Constitution and Procedure for the Prescription Medicines Code of Practice Authority will operate in respect of complaints received on and after 1 January 1996.

This issue of the Review sets out overleaf the major changes which have been made in the 1996 edition.

Clear complaints are appreciated

It is often difficult to be certain as to what exactly is being complained about in inter-company complaints.

Complaints which consist of a critical essay on a promotional item but which never really come to the point as to what allegations are being made are difficult to deal with and, as a consequence, particular aspects may not receive adequate attention.

A complaint should clearly set out the allegations which are made, preferably numbering the allegations when there is more than one. This makes the complaint easier to deal with.

Notification of signatories

Companies are reminded that Clause 14.2 of the Code of Practice requires that the names of those nominated for the certification of promotional material, together with their qualifications, should be notified in advance to the Product Information and Assessment Unit of the Post Licensing Division of the Medicines Control Agency and to the Prescription Medicines Code of Practice Authority. The names and qualifications of designated alternative signatories must also be given and changes in the names of nominees must be promptly notified.

Although some companies do ensure proper notification in this way others do not and companies are reminded of their obligation in this respect.

New Deputy Secretary joins the Authority

After having had only two members for nearly six months, the Authority has been brought back to its proper strength of three now that it has been joined by its new Deputy Secretary, Jane Landles.

As reported in the November Review, Jane was formerly a medical information officer and a nominated Code of Practice signatory with Zeneca Pharma.

Review available on Diskette

This edition of the Code of Practice Review can be made available on a Diskette in Word for Windows.

No charge will be made on this occasion but we are interested in assessing whether there would be a regular demand for having the material in such a format. Those wishing to have a copy should contact Emer O'Reilly at the PMCPA, telephone 0171-930 9677 extn 1443.

Marketing authorization numbers

In the 1996 edition of the Code of Practice for the Pharmaceutical Industry, references to "product licences" have been changed to references to "marketing authorizations". This is to reflect changing circumstances, such as the fact that products may now be approved by the European Medicines Evaluation Agency. A similar change has been made to The Medicines (Advertising) Regulations 1994 (SI 1994 No 1932).

This change in the Code does not mean that amendments are needed to the prescribing information in current promotional materials as some companies have assumed. If a product has a product licence then it remains entirely appropriate to refer to it as such.

Giving an undertaking

Paragraph 7.1 of the Constitution and Procedure for the Prescription Medicines Code of Practice Authority requires that a company which has been ruled in breach of the Code must ".... provide a written undertaking that the promotional activity or use of the material in question (if not already discontinued or no longer in use) will cease forthwith ....".

The Code of Practice Appeal Board has asked that companies be reminded that this means that use must cease at once. Journal advertisements must cease as soon as possible, due allowance being made for irrevocable appearances yet to come. The use of mailings and detail aids etc must cease immediately. They may not continue to be used until replacement material is available.

How to contact the Authority

Our address is:

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

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

Copies of the Code of Practice for the Pharmaceutical Industry and of this Review can be obtained from:

Emer O'Reilly on
0171-930 9677 extn 1443.

Direct lines can be used for the members of the Authority.

David Massam 0171-747 1405
Heather Simmonds
0171-839 1058

Jane Landles 0171-747 1415

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

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

Changes to the Code of Practice for the Pharmaceutical Industry

Companies are reminded that the following are the principal changes to the Code of Practice for the Pharmaceutical Industry which have been made in the new 1996 edition:

- the supplementary information to Clause 1.1 as to the applicability of the UK Code of Practice to international journals has been expanded and now states that journals which are produced in English in the UK are subject to the Code even if only a small proportion of their circulation is to a UK audience;

- the exemption from the Code in Clause 1.2 for replies made in response to individual enquiries from members of the health professions has been amended to make it clear that they are exempt only if they relate solely to the subject matter of the enquiry and are not promotional in nature; supplementary information is now given about such replies being drafted in advance;

- Clause 1.2 of the Code exempting from its application factual informative announcements etc has been amended so that the word "accurate" is included;

- the exemptions for measures or trade practices relating to prices, margins or discounts in the supplementary information to Clauses 1.2 and 18.1 has been amended to state that the practices in existence on 1 January 1993 must have been in existence in the pharmaceutical industry;

- Clause 1.6 now defines a "representative" to mean a representative calling on members of the health professions and administrative staff in relation to the promotion of medicines - the distinction between a "medical representative" and a "generic sales representative" is now set out in Clause 16.3;

- the ABPI Guidelines on the provision of non-promotional advance information about new products or product changes which were issued in 1992 have now been incorporated in a slightly modified form in the supplementary information to Clause 3.1;

- the minimum typesize for prescribing information which is recommended in the supplementary information to Clause 4.1 is now that the typesize should be such that a lower case letter "x" is no less than 1mm in height;

- an additional provision is added to Clause 4.2 concerning the fact that the information relating to dosage, method of use and side effects etc must be placed in such a position in the advertisement that its relation to the claims and indications for the product can be appreciated by the reader; this can normally be met by including all such information together in the prescribing information but companies should bear in mind that other pages should not be misleading in themselves and any limitations on the use of a product, for example that a product is licensed only as "add-on" therapy, should appear where the claims are made;

- the non-proprietary name of a product must be given immediately adjacent to the most prominent display of the brand name and this requirement has been amended so that the reference to a typesize of 10 point bold is changed to one of not less than 10 point bold;

- Clause 4.7 now clarifies that the date which must appear on promotional material is the date upon which the promotional material as a whole was drawn up or last revised - there has been some confusion on this point;

- the supplementary information to Clause 5.5 now confirms that telephone numbers are allowed in abbreviated advertisements;

- the previous voluntary agreement that no issue of a journal should bear advertising for a particular product on more than three pages has now been incorporated in the Code as Clause 6.4 and further supplementary information on the matter clarifies the position of inserts;

- the supplementary information to Clause 7.2 relating to economic evaluation now states that to be acceptable as the basis of promotional claims, the assumptions made in an economic evaluation must be clinically appropriate and consistent with the

marketing authorization;

- Clause 9.1 relating to the special nature of medicines and the professional standing of the audience to which materials and activities are directed has been amended and now states that promotional materials and activities must not be likely to cause offence and that high standards must be maintained at all times;

- Clause 9.7 and its supplementary information have been amended so that reply paid cards which are intended to be sent through the post back to a company may bear both the name of the medicine and information as to its usage in the case of those medicines which may legally be advertised to the general public but not otherwise;

- Clause 9.8 has been amended so that e-mail may not be used for promotional purposes except with the prior permission of the recipient;

- the provision relating to the sponsorship of meetings formerly in Clause 9.9 is now Clause 19.3;

- Clause 11.1 clarifies the question of the provision of unsolicited copies of articles in journals - the articles themselves must have been refereed;

- Clause 13 relating to the scientific service has been expanded;

- the supplementary information to Clause 14.1 now states that promotional aids must be certified in accordance with the normal procedure;

- the supplementary information to Clause 14.4 now includes information on the need to keep certain information about promotion beyond the three year limit which applies in relation to Clause 14.4 itself;

- a new clause, Clause 15.5, states that in an interview, or when seeking an appointment for one, representatives must at the outset take reasonable steps to ensure that they do not mislead as to their identity or that of the company they represent;

- considerable changes have been made in Clause 16 to the requirements for representative examinations; the new requirements are intended to ensure that all representatives have to take an examination whereas under the previous Code certain representatives did not;

- the supplementary information to Clause 17 now states that titration packs are not regarded as samples;

- the supplementary information to Clause 17.3 now states that signed and dated written requests for samples must be retained for not less than one year;

- Clause 17.9 has been expanded to require companies to have an adequate system of control and accountability in relation to samples;

- Clause 17.10 deals with medicines sent through the post;

- a new clause, Clause 17.11, provides that unsolicited medicines must not be supplied to the general public;

- the supplementary information to Clause 18.1 refers to the acceptability of fair and reasonable package deals;

- the supplementary information to Clause 19.1 clarifies that the payment of reasonable honoraria and reimbursement of out of pocket expenses, including travel, for speakers, is permissible;

- the supplementary information to Clause 19.1 now refers to circumstances in which administrative staff may be invited to meetings;

- the wording of Clause 20.1 prohibiting the advertising to the public of medicines which may not legally be advertised to the general public has been clarified;

- the supplementary information to Clause 20.2 now refers to financial information made available to shareholders etc;

- a new clause, Clause 20.5, states that companies are responsible for information about their products which is issued by their public relations agencies;

- an entirely new clause, Clause 21, provides that when an undertaking has been given in relation to a ruling under the Code, the company concerned must ensure that it complies with that undertaking - failure to comply was previously dealt with as a repeat of the original breaches.

Changes to the Constitution and Procedure for the Prescription Medicines Code of Practice Authority

The following are the principal changes made in the 1996 edition:

- the Prescription Medicines Code of Practice Authority no longer has retained advisers but will take advice from whomsoever it considers appropriate (Paragraph 2.3);

- if a quorum cannot be obtained by the Code of Practice Appeal Board for the consideration of a case because of the number of members barred due to their companies' interest in the case, or for any other reason, the Chairman may co-opt appropriate persons so as to enable a quorum to be achieved (Paragraph 4.2);

- a copy of the response to a complaint is to be provided to a complainant whose complaint has been rejected so that they are in a better position to decide whether or not to appeal (Paragraph 7.2);

- the complainant who appeals will have an opportunity to comment upon the respondent company's response to the appeal (Paragraph 7.4);

- the Code of Practice Appeal Board now has the power to require an audit of a company's procedures in relation to the Code to be carried out by the Prescription Medicines Code of Practice Authority (Paragraph 10.4);

- the respondent company and the medicine concerned will be named in all case reports, whether or not a breach of the Code has been found (Paragraph 12.2);

- companies, organisations and official bodies will be named in case reports but the information given will not be such as to identify any individual person (Paragraph 12.2);

- both parties to a case will have an opportunity to comment upon a case report (Paragraph 12.3);

- the position as to the withdrawal of appeals by respondent companies has been clarified (Paragraph 14.3);

- where two or more companies are ruled in breach of the Code in relation to a matter involving co-promotion, each company will be separately liable to pay an administrative charge (Paragraph 15.3).

CODE OF PRACTICE TRAINING

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

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

Forthcoming Code of Practice seminar dates are:

Monday, 1 April 1996
Monday, 13 May 1996
Wednesday, 26 June 1996

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

For further information regarding any of the above, please contact Emer O'Reilly at the PMCPA for details (0171-930 9677 extn 1443)

CASE AUTH/315/6/95

SMITHKLINE BEECHAM v PFIZER

Lustral detail aids

SmithKline Beecham complained about hospital and general practitioner detail aids on Lustral issued by Pfizer. There were six allegations in total. It was alleged that too much space was devoted to an issue of limited clinical significance, that only interactions with CYP 2D6 had been referred to, that fluvoxamine had been omitted when comparing inhibitory potential for CYP 2D6, that a list of drugs metabolised by the P450 2D6 enzyme system was inaccurate and misleading, that a suggestion that Lustral had the least potential for drug interactions and was therefore the safest of all the SSRIs was inaccurate and that certain data had been misleadingly presented. A breach of Clause 2 was also alleged.

The Panel ruled that, in a part of the detail aid which appeared to deal with drug interactions generally, the reference only to interactions with P450 2D6 was misleading; no attempt had been made to put this in the context of other potential pharmacokinetic mechanisms and their clinical relevance. The listing of drugs metabolised by the P450 2D6 enzyme system was ruled to be misleading and inaccurate as some of the products should not have been included and only certain products in the drug classes mentioned were so metabolised. Data presented in a bar chart was ruled to be misleading as it did not reflect the situation as a whole. Pfizer accepted the first two of these rulings but appealed the third which was overturned upon appeal by the Appeal Board.

No breach was ruled by the Panel in relation to the other three allegations, these being in respect of the amount of space devoted to the issue, the omission of any reference to fluvoxamine when comparing inhibitory potential for P450 2D6 and the claim that Lustral had the least potential for drug interaction. It was also ruled that there had been no breach of Clause 2.

SmithKline Beecham Pharmaceuticals UK complained about promotional material for Lustral (sertraline) issued by Pfizer Limited. The items in question were a hospital detail aid, reference 66276Mar95, and a GP detail aid, reference 66275Mar95. The degree of emphasis placed upon the small differences between sertraline and the other SSRIs in their potential to inhibit CYP 2D6 was, in SmithKline Beecham's view, inaccurate, misleading and disparaging of paroxetine (its product, Seroxat). In addition to its detailed allegations, SmithKline Beecham alleged that the unbalanced nature of the promotion might lead to inappropriate prescribing and therefore represented a breach of Clause 2. SmithKline Beecham referred to the hospital detail aid in its complaint and said that several of the allegations also applied to the GP detail aid.

1 Amount of space devoted to an issue of alleged limited significance

COMPLAINT

SmithKline Beecham said that three pages of the detail aid were devoted to discussing the issue of theoretical interactions between selective serotonin reuptake inhibitors (SSRIs) and drugs metabolised by CYP 2D6. This represented one quarter of the hospital detail aid. To devote such a large amount of space to an issue which was of limited clinical significance imbued it with a degree of importance which it did not deserve and as such was both inappropriate and misleading. A breach of Clause 7.2 was alleged.

RESPONSE

Pfizer said that there were in fact only two pages directly discussing or presenting experimental results of SSRIs and cytochrome P450 2D6. As a matter of principle, Pfizer did not accept that counting pages was a relevant basis for reviewing compliance with the Code. In Pfizer's view, the substance of the relevant copy should be addressed. Pfizer did not consider that two to three pages in a twelve page detail aid was excessive. Furthermore, it disagreed with the reference to "limited clinical significance" for the potential of any drug interaction mediated through the cytochrome P450 2D6. Pfizer had made it clear in the detail aid that the clinical significance of the data had yet to be established but Pfizer did not accept that it was not of clinical interest.

RULING

The Panel noted that the detail aid consisted of a total of twelve pages and that two pages were specifically devoted to the question of interactions between SSRIs and drugs metabolised by cytochrome P450 2D6. It was not considered that this was excessive and the number of pages was not in any event the sole criterion. It was ruled that there had been no breach in this regard. The question of clinical relevance was the subject of point 2 below.

2 Reference only to interactions with CYP 2D6

COMPLAINT

SmithKline Beecham said that the first of the three pages of the detail aid relating to drug interactions asked the question "How many of your patients will be taking other medicines?", thus raising the issue of potential drug interactions in general. However, the rest of the detail aid referred only to theoretical interactions with CYP 2D6. This singular focus suggested that CYP 2D6 was the only factor to consider when discussing the issue of potential drug interactions and failed to adequately identify the potential for sertraline to interact with a variety of other commonly prescribed agents through a variety of different mechanisms (such as pharmacodynamic interactions - MAOIs, warfarin etc - and other pharmacokinetic interactions involving the 3A4 and 2C8/9/10 enzymes for example). The presentation also

failed to recognise the contributions of N-desmethylsertraline and norfluoxetine to CYP 2D6 inhibition. Thus the data presented an unbalanced view of the potential for drug interactions, particularly with sertraline, and was therefore misleading. A breach of Clause 7.2 was alleged.

RESPONSE

Pfizer said that the first page to which reference had been made was no more than an introductory question. Pfizer rejected the assumption that the detail aid suggested that cytochrome P450 2D6 was the only mechanism for potential pharmacokinetic drug interactions and it did not consider that those to whom it was addressed would interpret it in that way. Pfizer added that on the page headed "Cytochrome P450 2D6 - Drug interactions" reference was made both to the prescribing information appearing on the back page and that further information on interactions could be found in the Lustral data sheet.

RULING

The Panel noted that the reader would be alerted to consider interactions between Lustral and other medicines by the inclusion of the question "How many of your patients will be taking other medicines?" which was followed by detailed information on P450 2D6 inhibition. The Panel considered that the emphasis on P450 2D6 by itself suggested that this was the dominant and most important mechanism of drug interactions. No attempt had been made to set this in the context of other potential pharmacokinetic mechanisms and their clinical relevance. The Panel considered that the material was misleading as alleged and ruled that there had been a breach of Clause 7.2.

3 Omission of fluvoxamine when comparing inhibitory potential for CYP 2D6

The section at issue was headed "*In vitro* studies have shown that Lustral has a relatively low potential for P450 D6 inhibition compared to paroxetine or fluoxetine" under which appeared an arrow pointing downwards to indicate decreasing potential for P450 2D6 inhibition. In decreasing order, paroxetine, fluoxetine and Lustral were named.

COMPLAINT

SmithKline Beecham said that the material omitted to mention fluvoxamine which in fact had less of an inhibitory potential for CYP 2D6 than sertraline. By omitting this SSRI it suggested that sertraline was the least inhibitory of the SSRIs and the least likely to cause problems in this regard. This was clearly not the case and was misleading. Breaches of Clauses 7.2 and 7.6 were alleged.

RESPONSE

Pfizer said that comparison was made between fluoxetine, paroxetine and sertraline which were by far the most widely used SSRIs. The comparison was therefore pertinent. Pfizer did not accept that there could be any implication that all SSRIs were referred to. Pfizer said that this point had been raised in respect of an earlier detail aid in Case AUTH/255/12/94 and Pfizer had taken particular care to ensure that its new copy, which was the subject of the current complaint, would comply with the Panel's decision in that case.

RULING

The Panel noted that the detail aid clearly said that *in vitro* studies had shown that Lustral had a relatively low potential for P450 2D6 inhibition compared to paroxetine or fluoxetine. The Panel did not consider that this was misleading even though it was true that there was another product, fluvoxamine, which had an even lower potential for inhibition. The Panel noted that the promotional item which had been the subject of Case AUTH/255/5/94, referred to by Pfizer in its response, had compared Lustral with other SSRIs in general and the omission of any reference to fluvoxamine had been held to be in breach of the Code. It was considered that the current claim was acceptable and it was ruled that there had been no breach.

4 Listing of drugs metabolised by the P450 2D6 enzyme system

Beneath the arrow referred to in 3 above, was a heading "Commonly prescribed drugs metabolised by the P450 2D6 enzyme system include:" followed by a list containing both individual drugs and classes of them.

COMPLAINT

SmithKline Beecham said that two of the listed drugs, quinidine and phenytoin, stated to be metabolised by the P450 2D6 enzyme were not so metabolised. In addition it was stated that only certain beta blockers were metabolised by CYP 2D6. This was true, but it was also true of only certain tricyclic antidepressants, certain phenothiazines and certain type 1c antiarrhythmics. Pfizer had omitted to use the word "certain" before these groups of drugs giving the impression that all drugs in the classes mentioned were metabolised by CYP 2D6 and likely to interact with SSRIs. This was inaccurate and misleading in breach of Clause 7.2.

RESPONSE

Pfizer accepted the allegation regarding quinidine and phenytoin and future material would not make reference to these. Although it was known that quinidine did interfere with cytochrome P450 2D6 metabolism, it did accept that neither quinidine nor phenytoin should be referred to in this context. Their inclusion in the list had been based on inappropriate interpretation of the literature and consequential contravention of the Code was inadvertent.

The word "certain" did not appear before tricyclic antidepressants, phenothiazines and type 1c antiarrhythmics because those not metabolised had little clinical relevance. The most clinically important tricyclics, phenothiazines and type 1c antiarrhythmics were metabolised through the cytochrome P450 2D6 system. The word "certain" appeared before "beta blockers" because there were clinically important beta blockers

which were not so metabolised.

RULING

The Panel noted that it had been accepted by Pfizer that quinidine and phenytoin ought not to have been referred to as being metabolised by the P450 2D6 enzyme system and that they would be omitted in the future. The Panel did not accept Pfizer's contention that tricyclic antidepressants not metabolised through the P450 2D6 system had little clinical relevance because it understood that dothiepin, a commonly used tricyclic antidepressant, was not among the tricyclic antidepressants metabolised by P450 2D6. The Panel considered that the section gave the impression that all the drugs in the classes mentioned were metabolised by the P450 2D6 enzyme system and this was not so. An unqualified statement should not be used in relation to any class where there were exceptions which were in clinical use. The Panel considered that the section was misleading and inaccurate. A breach of Clause 7.2 was ruled.

5 Suggestion that Lustral had the least potential for drug interactions and was therefore the safest of all the SSRIs

COMPLAINT

SmithKline Beecham said that the detail aid claimed that differences in potential to inhibit CYP 2D6 might affect drug interaction potential. A list of drugs metabolised by CYP 2D6 was thereafter included. The implication was that there might be a risk of clinically significant interactions between the SSRIs and these drugs, but that Lustral had the least potential and was therefore the safest of all the SSRIs. Published data did not demonstrate any clinical relevance to differences in inhibitory potential except for certain tricyclic antidepressants (eg desipramine and nortriptyline) and to infer that there might be a clinical benefit for one SSRI over the others for all CYP 2D6 substrates was premature.

In short, the inferred clinical benefit had not been established for anything other than certain tricyclics and the way the data was presented misled as to the potential for Lustral to interact with the CYP 2D6 enzyme. This was not only inaccurate but potentially dangerous because it might lead to complacency in respect of the potential of sertraline to cause interactions. Those studies and case reports that had been published regarding possible CYP 2D6 drug interactions implicated sertraline as well as paroxetine and fluoxetine. Breaches of Clauses 7.2, 7.3 and 7.8 were alleged.

RESPONSE

Pfizer submitted that the detail aid made it clear when introducing the area of cytochrome P450 2D6 drug interactions, that "While the clinical significance of the following data is yet to be established, differences exist between Lustral, paroxetine and fluoxetine in their inhibition of cytochrome P450 2D6 which may affect drug interaction potential". The bar charts included on the next page of the detail aid described the small effect which sertraline had on cytochrome P450 which was significantly less than was produced by both paroxetine and fluoxetine. [Note: the bar charts are described in detail under Point 6 below].

Pfizer stated that SmithKline Beecham also referenced isolated case reports on drug interactions with desipramine and sertraline. It suggested that this was an indication for the inhibition of sertraline on the cytochrome P450 2D6 system. A minor effect of sertraline might be expected as clearly indicated in the bar charts presented on the second page relating to cytochrome P450 2D6 inhibition. Isolated case reports might be suggestive of a potential drug interaction. However, they provided no information regarding the incidence and the magnitude of the event. The limitation of isolated case reports rested with the uncontrolled and limited information regarding specific compliance. Further the reference cases failed to describe the basic metabolic phenotype of the patients involved, so failing to identify the clinically relevant metabolic characteristics of the patients involved. The extent of the drug interaction was either over or underestimated in isolated case reports and certainly isolated cases did not equate to rigorously conducted pharmacokinetics studies.

In relation to the dismissal of the use of desipramine as a suitable probe to evaluate cytochrome P450 2D6 interaction potential, Pfizer said that for desipramine, the cytochrome P450 2D6 represented the major route of clearance. It was therefore appropriate to extrapolate that any drug modifying the metabolism of desipramine, by inhibition or acting as a substrate for cytochrome P450 2D6 would also modify the hepatic metabolism and clearance of other drugs metabolised through the same route. With this evidence, and standard practices in pharmacological research, Pfizer did not accept the suggestion that the effect of sertraline on cytochrome P450 2D6 metabolism was limited to desipramine and nortryptyline.

RULING

The Panel considered that overall the implication was that Lustral might exhibit advantages over fluoxetine and paroxetine but having reviewed the submissions and evidence from both parties decided that what had been said and its presentation were not unreasonable and ruled that there had been no breach of the Code.

The Panel noted that the bar charts which had been referred to by Pfizer were considered under point 6 below.

6 Misleading presentation of data

Data from two studies were presented in bar charts on the page in question. One study, headed "Percentage increase in desipramine levels after 21 days' joint therapy", was an open-label parallel study in which healthy volunteers received desipramine (50mg daily) alone for seven days followed by desipramine plus either Lustral (50mg daily) or fluoxetine (20mg daily) for a further 21 days. The second study, headed "Increase in desipramine levels (AUC) after 10 days' joint therapy with LUSTRAL or paroxetine", was an open, crossover study in which healthy volunteers received desipramine (50mg daily) plus either Lustral (50mg daily for 10 days then 100mg daily for 3 days) or paroxetine (20mg daily for 10 days then 30mg daily for 3 days).

COMPLAINT

SmithKline Beecham alleged that the presentation of this data was misleading. Steady state levels of sertraline and its important metabolite N-desmethylsertraline were unlikely to have been achieved in the crossover study with paroxetine because the initial dosing period only lasted 10 days. It could take at least 14 days to reach steady state for N-desmethylsertraline because of its long half life. Thus the combined effect of sertraline and N-desmethylsertraline on the desipramine plasma levels was likely to have been underestimated. For the same reason, the final three days of sertraline dosing at 100mg would also significantly underestimate any further effect on desipramine levels.

The average daily dose of sertraline used in clinical practice was not 50mg. Several studies showed that the average dose was in excess of 70mg daily and was more likely to be 100mg or greater. Higher doses had been associated with a threefold increase in plasma desipramine levels (Zussman BD *et al*) and thus the potential for sertraline to be associated with drug interactions with desipramine in clinical practice was considerably underemphasised by the detail aid.

Case reports had indicated that sertraline at 50mg was associated with clinically significant CYP 2D6 interactions (Barros J and Assnis G). In addition, any drug interactions that might occur with sertraline might be prolonged because of the half life of its metabolite and the magnitude of the interaction might increase with dose (Lustral data sheet and Zussman). Thus clinically relevant *in vivo* data was omitted from the detail aid.

In short, the potential for sertraline to increase plasma levels of desipramine had been presented in a misleading manner. Even though case reports existed which indicated that sertraline at 50mg daily was associated with significant drug interactions, this data was not presented in the detail aid and thus clinicians were given a selected and biased view of the issue. The clinical relevance of increased plasma levels of desipramine had been reported (Glassman AH *et al*) but the extent to which the SSRIs altered the plasma levels of the other CYP 2D6 substrates had yet to be established. The implied generalisation that paroxetine (or fluoxetine) could interact with a wide range of CYP 2D6 substrates to a clinically significant extent therefore remained highly speculative, not having been substantiated with direct experimental data.

RESPONSE

Pfizer said that the usual therapeutic dose of sertraline was clearly described in the Lustral data sheet as 50mg daily. This was supported by broad clinical experience with sertraline in the treatment of depression. Although SmithKline Beecham made general reference to both the referenced studies (Alderman, 1994, and Preskorn, 1994) Pfizer confined its detailed comments to the Alderman case as a comparison with paroxetine seemed to be the focus for the complaint. It could comment similarly on the Preskorn paper if necessary.

From a theoretical perspective, a drug or metabolite on a fixed dose schedule approached steady state, reaching 50% of steady state after one half life (T ½), 75% after 2 T ½, 87.5% after 3 T ½, 94% after 4 T ½ and 97% after 5 T ½. In the study by Alderman, both sertraline and paroxetine had a T ½ of approximately one day and N-desmethylsertraline a T ½ of about three days. Based on this, after 10 days of daily dosing at the lower dose (study days 8 to 17) sertraline and paroxetine would reach steady state after 5 days = 5 T ½. While N-desmethylsertraline would take longer, it would have reached at least 90% of steady state on study day 17, which was when the low dose pharmacokinetic assessments were carried out This was based on the fact that 10 days was approximately 3.3 T½ for N-desmethylsertraline. Therefore, the overall inhibitory impact after 10 days of sertraline (at study day 17) would have reached approximately 95% of its steady state maximum.

An empirical test suggested that this analysis for sertraline and N-desmethylsertraline held true. Pfizer supplied additional data, which were not included in the original presentation of the Alderman study since they were not available at the time.

While it was argued that the 10 day dosing period might underestimate the combined effects of sertraline and N-desmethylsertraline on desipramine plasma levels, both empirical and theoretical analyses supported the conclusion that the degree of underestimation was probably insignificant from a practical or clinical point of view.

In relation to the comment from SmithKline Beecham that the final 3 days of sertraline dosing at 100mg had also significantly underestimated any effect on desipramine levels, Pfizer said that in the case of the higher dose, 3 days were not adequate to properly evaluate either SSRI. The three day period was chosen because it wished to explore safely, by using a short period, whether unexpectedly large doses of desipramine were likely to occur with an SSRI dose increase above the minimum while keeping the overall study length (61 days) within reasonable limits. For this reason, the abstract did not present or discuss the higher dose level data except to comment that the relationships seen at lower doses were not altered. It needed to be noted however that paroxetine was also highly unlikely to achieve steady state in the same 3 days because of its recognised non-linearity at higher dose levels and its observed non-linear behaviour even at the lower dose levels under the conditions of the paper by Alderman.

PANEL RULING

The Panel noted that the bar charts in question appeared opposite the page which had been the subject of criticism in points 3, 4 and 5 above. They compared the percentage increase in desipramine levels after joint therapy with Lustral and fluoxetine and with Lustral and paroxetine. In the comparison between Lustral and fluoxetine the respective levels were 23% and 480%. In the comparison between Lustral and paroxetine the respective levels were 37% and 421%.

The Panel understood that studies which found the average use of higher doses of sertraline than 50mg had been carried out in the United States where higher doses tended to be used more frequently than in the UK. There was support for the view that in the UK it was reasonable to take 50mg as the dose. The Panel noted that Zussman *et al* had recently reported a study in healthy male

volunteers showing plasma concentration of desipramine increases up to three fold in those subjects achieving high steady state plasma concentrations of sertraline and N-desmethylsertraline. Doses of 150mg of sertraline had been given. No untoward side effects had been noted and the clinical relevance of such increases had not been demonstrated. Nevertheless, this recent evidence for interaction between sertraline and desipramine at higher plasma levels of sertraline had not been reflected in the detail aid.

The Panel considered that what was actually said in the bar charts was true as far as it went but was of the opinion that the impression given did not reflect the situation as a whole and was unbalanced. A breach of Clause 7.2 was ruled.

This was appealed by Pfizer.

APPEAL BY PFIZER

Pfizer disagreed with the conclusion and ruling of the Panel for the following reasons:-

a The presentation of the data was fair and balanced and referred to comparative data of the most widely used clinical dose for sertraline 50mg, and for paroxetine and fluoxetine 20mg respectively.

b The study presented in the paper by Zussman *et al* was non comparative.

c The paper by Zussman *et al* referred to a high daily dose, 150mg, of sertraline which was administered in clinical practice only in a very small minority of patients (only 3% of prescriptions were for daily doses above 100mg, IMS Data,Year to mid 1995).

d Higher doses of sertraline still produced a smaller inhibition of desipramine clearance mediated through the CYP 2D6 system than paroxetine and fluoxetine at their respective starting dose of 20mg daily.

e The inhibition of the hepatic clearance of desipramine induced by the higher dose of sertraline at 150mg produced no untoward side effects.

The study by Zussman *et al* investigated the effect of the high dose of 150mg sertraline administered with desipramine on the activity of the hepatic CYP 2D6 system by measuring the change in desipramine clearance rate. This study demonstrated a modest increase in the desipramine AUC (area under the curve), from baseline, of 66%.

The study by Alderman *et al* showed that a dose of paroxetine 20mg increased the AUC of desipramine to a value of 421%. Similar results were found by Preskorn when measuring the effect of fluoxetine 20mg on the clearance of desipramine. In this case the desipramine AUC was increased to a value of 380%. As it happened even at the high dose of sertraline, 150mg daily, the effects on the CYP 2D6 mediated desipramine clearance mechanism were still very substantially less than those observed for both fluoxetine and paroxetine at their respective starting dose of 20mg daily. However, this would not, in Pfizer's view, be a reasonable basis for presenting the data as it would not be a fair comparison.

Theoretically, Pfizer might compare a high 150mg dose of sertraline with proportionately high doses of paroxetine and fluoxetine. In such an event, Pfizer would confidently predict that the comparative data would show differences on a *pro rata* basis at least as great as appeared in the comparative data in its detail aids. In practice, it would not be appropriate to carry out such comparative high dose trials on ethical grounds.

The inhibitory effects on the CYP 2D6 enzyme system were concentration dependent. Because of their non linear pharmacokinetics, both paroxetine and fluoxetine were expected to inhibit the activity of the hepatic isoenzyme with disproportionately high concentrations of paroxetine and fluoxetine, and their metabolites. For example the clearance of desipramine might increase in an unpredictable fashion, a situation unacceptable in clinical practice.

Pfizer said that the figure of 480% given in the detail aid for fluoxetine had turned out to be erroneous. It should have been 380%. This had arisen as a result of a *bona fide* but erroneous interpretation of the report in question. Pfizer did not consider that this affected its submissions in the appeal but the Appeal Board should be aware of the information. In the meantime, Pfizer was at once advising its sales force of the position regarding these figures.

APPEAL BOARD RULING

The Appeal Board accepted Pfizer's submission that the data from the Zussman *et al* paper did not need to be reflected in the chart in question and ruled that there had been no breach of the Code.

The appeal therefore succeeded.

Alleged breach of Clause 2

SmithKline Beecham had also alleged that the unbalanced nature of the promotional material might result in inappropriate prescribing and therefore represented a breach of Clause 2. The Panel did not consider that there had been a breach of Clause 2 and ruled no breach in this regard.

Complaint received **29 June 1995**

Case completed **15 November 1995**

CASE AUTH/316/7/95

ETHICS COMMITTEE CHAIRMAN v SERVIER

Study using Coversyl and Natrilix

The chairman of a local research ethics committee complained about Servier's multicentre study comparing patient self measurement of blood pressure with measurement by their general practitioners. The committee was concerned that the trial protocol insisted that all patients had to use Servier's products, Coversyl and Natrilix. It considered that the trial had a second unstated objective, namely to transfer patients to these products.

The Panel found it difficult to accept the need for standardisation of therapy in the study which was concerned not with the merits of any particular preparation but with blood pressure measurement. It decided that the study amounted to the promotion of Coversyl and Natrilix. A breach of Clause 10.2 was ruled as the study was disguised promotion. Although the actual level of payment to doctors was not unreasonable, as the study had been ruled to be promotional, it followed that the payments were inappropriate and a breach of Clause 18.1 was also ruled. The Appeal Board upheld this ruling following an appeal by Servier.

COMPLAINT

The chairman of a local research ethics committee complained about Servier Laboratories Ltd's multicentre trial "Comparison of patient self measurement of blood pressure using automatic sphygmomanometers with GP measurements and its relevance to therapeutics decision making". This trial had been submitted to the committee for approval by a local general practitioner. The complainant understood that the general practitioner was to be paid £300 per patient entered. The ethics committee was concerned that, in spite of the title of the study and the declared objective, the trial protocol insisted that all patients were changed on to particular antihypertensive drugs. The complainant had spoken to the medical director of the ABPI who felt, as they did, that this study had a second unstated objective, namely to transfer patients on to the company's drugs and had suggested that the trial protocol was sent to the Authority for its opinion and possible action.

RESPONSE

Servier Laboratories Ltd, although not a member of the ABPI, had nevertheless agreed to comply with the Code. The company said that when the study was planned it had sought and obtained independent ethical committee approval from the Royal College of General Practitioners (RCGP). At that time the RCGP made several points regarding the details of the study, all of which were answered to its complete satisfaction. It was only when this RCGP approval had finally been obtained that Servier felt in a position to launch this interesting and useful study.

Servier submitted that the study had a valid scientific rationale. It was well known that blood pressure values obtained on an occasional basis at the doctor's surgery might lead to a false estimation of blood pressure and its variability, whereas blood pressure values obtained by automeasurement had greater reproducibility. Thus automeasurement might be a useful tool in assessing "borderline" or "white coat" hypertension and also for evaluating the efficacy of antihypertensive therapy. The ultimate benefit of automeasurement might then mean treating fewer patients but with more appropriate therapy. The study therefore proposed to evaluate the impact of training in automeasurement as well as the repercussions of this training on control of hypertension in the long term, in daily practice, on a representative sample of the general UK population with hypertension.

Turning to the points raised by the complainant, the first of these being that the GP was to be paid £300 per patient entered, Servier pointed out that the financial protocol for the study stated quite clearly that the maximum amount payable for participation in the study was £300 (which corresponded to £60 per patient) plus the supply of two automatic blood pressure monitors with a total retail value of £280. Thus the overall "payment" for the inclusion and completion of five patients was £580. This equated to a payment of £116 per patient for time over and above that required for normal patient care ie almost one hour (at current BMA rates).

The second point was that the trial protocol insisted that all patients were changed on to particular antihypertensive drugs.

Servier pointed out that the criteria for the selection of patients for the study were adult men or women aged over 18 years:

- suffering from essential hypertension (supine DBP found on at least three occasions to be between 91 and 115mmHg without antihypertensive treatment)
- treated with monotherapy, other than perindopril (Coversyl) but either poorly controlled (DBP > 90mmHg) or normalised (DBP < 90mmHg) but at the price of suffering from side effects interfering with patient compliance.
- informed of the objectives of the study and agreed to participate in writing.

Therefore no hypertensive patient who was both well controlled and tolerating their current therapy was eligible for the study. Thus no patient would have their clinically acceptable treatment changed.

As part of the secondary aims of the study, Servier would be assessing patients' blood pressure profiles (from their automeasurement values) to see how they varied throughout the day. Levels of activity and stress would be recorded and any correlation between home and surgery figures would be analysed. In order, therefore, to minimise the number of controlling variables a standardised treatment regime had been specified.

The choice of perindopril as that standard treatment was taken based upon some further considerations:

(i) As Servier intended to include a large cross section of hypertensive patients (elderly, diabetic, hyperlipidaemic etc) it was argued that a "uniformly acceptable" treatment was required. The most appropriate choice Servier thought was an ACE inhibitor as the contraindications for its use were minimal, the side effect profile would be acceptable to the patients and the clinical efficacy would be of a required standard.

(ii) As the manufacturer of perindopril, Servier had specified its use in the research protocol (rather than any other drug) because it was then in a position to:

- supply the study medication (as it was obliged to do as a sponsor in a clinical trial)

- extend its clinical trial indemnity to cover the study as a further safeguard to patients taking part.

The final point raised by the complainant was that the study had a second unstated objective, namely to transfer patients on to Servier's products. The company submitted that its previous answers dealt with this comment but stressed that there was absolutely no compulsion for the investigator to continue his patient on perindopril once the study was finished. It should be made absolutely clear that there existed no inducement, either financial or by way of providing free drug beyond the duration of the study, to the general practitioner to continue prescribing perindopril.

Servier said that it was intended to recruit 400 "centres" (either individual general practitioners or several general practitioners within one surgery). Each centre would then be asked to recruit 5 patients. As at 5 July, the study had received approval from 34 ethics committees which were responsible for 98 centres. Patient recruitment had already started in these 98 centres. Servier was awaiting a response from a further 53 ethics committees who were in turn responsible for 150 centres.

In response to the Authority's request for the justification as to the reasons for recruiting two thousand patients, Servier said that initially it took advice from its internal statistics department. It said that as the study had no "hard" clinical end points and was looking principally at attitudes to and acceptance of automeasurement, the study should be regarded as epidemiological in nature. To that end Servier had aimed to recruit both general practitioners and patients of differing backgrounds in sufficient numbers to enable it to draw some conclusions about not only the type of patient (social background, age, cardiovascular profile etc.) but also the type of general practitioner (inner city, urban, rural) that would be both amenable to the technique and would also benefit from it. Therefore, as a large scale epidemiological project without a definite clinical end point it was not possible to calculate a precise patient number which would either prove or disprove the rationale. The RCGP had made several comments and had asked for amendments to the protocol. Amongst those comments it raised the issue of doctor and patient selection, study numbers and final study analysis. All the questions were answered to the RCGP's satisfaction.

In relation to the possibility of a breach of Clause 10.2, Servier said that in its view the valid scientific objective of the study meant that it did not fall in any of the activities mentioned in that clause. Furthermore, clinical end points which could be linked to its product were not the primary focus of the study. No promotional claims were made either in the introductory letter to participating general practitioners or within the protocol itself. There was no branding, either corporate or product related, on the monitors provided for the study. It should be stressed that it was hoped that the results from the study, when published, might benefit the general practitioners and patients in providing information on a relatively simple technique which might obviate the need for treatment in an important percentage of so called "hypertensive patients".

PANEL RULING

The Panel noted that the study was entitled "Comparison of patient self measurement of blood pressure using automatic sphygmomanometers with GP measurements and its relevance to therapeutics decision making". The Panel further noted that Servier had stated that the protocol had been approved by the Ethics Committee of the RCGP. The Panel noted that the financial protocol stated that the technical protocol had been approved by the RCGP. Although the objective of the study was concerned with the accuracy of blood pressure measurements, it involved patients' medication being perindopril (Servier's Coversyl) supplemented, if necessary, by indapamide (Servier's Natrilix) and it would thus come within the scope of the Code if it were to be found that it was promotional in nature.

Turning first to the question of payment for the study, the Panel noted that a doctor would be paid £60 per completed case, making a total of £300 for the five cases which each doctor was expected to identify. In addition, each doctor would receive two Omron HEM-705CP Automatic Oscillometric Digital Blood Pressure Monitors to use in the study. The retail price of these was £140 each according to Servier. The Panel noted that the complainant had been under the impression that £300 per patient was to be paid but this was not so. It seemed to the Panel to be reasonable to allow one hour of the doctor's time per case and the level of payment was acceptable as being in line with British Medical Association suggested fees. Whether any payment at all was appropriate, however, depended upon whether the study as a whole was acceptable.

The Panel then turned to the question of the place of perindopril and indapamide in the study. It was noted that patients entering the study had to have newly diagnosed mild to moderate hypertension or to have had previous treatment with monotherapy but not properly controlled or to have been normalised with monotherapy but with side effects interfering with patient compliance. It was obligatory for patients entering the study to be on perindopril with the addition of indapamide if required.

The Panel noted that protocol said that "In order to obtain maximum homogeneity and to give the automeasurement apparatus a high degree of sensitivity, the greatest uniformity possible is sought by only including patients in this study who receive a standardised treatment". The Panel had difficulty in accepting that standardised treatment was necessary for the study which was

concerned not with the merits of any particular preparation but with a comparison of blood pressure measurements taken in the surgery with those taken by patients themselves in their own homes. Nothing that had been said by Servier convincingly justified the need for standardised therapy. The reasons given by Servier for choosing perindopril and indapamide as the standardised therapy were that Servier's liability insurance would then cover the study and that it was easier to supply the products to participating doctors if they were their own. The Panel noted that if standardised treatment had not been required, patients could have been entered into the study whilst taking treatment prescribed in the usual way and there would have been no need for Servier to supply the therapy. Servier's comment that the doctor was under no obligation to continue to prescribe perindopril when the study was over was true but of little import. A patient being successfully treated with perindopril would clearly not be taken off it.

Given the purpose of the study, the Panel found it difficult to accept the need for standardisation of therapy. The Panel decided that the study amounted to the promotion of Coversyl and Natrilix. The Panel therefore ruled a breach of Clause 10.2 of the Code which prohibits the use of studies as disguised promotion. Although the actual level of payments for participation in the study was not unacceptable, as the study was ruled to be disguised promotion it followed that the offer of such payments was inappropriate. The Panel therefore also ruled a breach of Clause 18.1.

APPEAL BY SERVIER

Dealing first with the scientific rationale for the study, Servier said that previously published studies had demonstrated the potential of patient blood pressure automeasurement to confirm the presence (and indeed the severity) or absence of hypertension and the need to treat. Furthermore, improvements in patient follow-up, compliance with treatment and reduction in GP visits had all been noted with patient automeasurement. However, these studies were generally small scale or questionnaire based and it had been felt that a large UK based study would hopefully be able to provide confirmation of these previous results. Indeed, Servier's study intended, via patient subgroup analysis, to try and identify more clearly which patients might be best suited to this monitoring technique.

Servier's interest in automonitoring/automeasurement and disease management as a whole was not new and stemmed from its previous funding of a successful study by Shaw *et al* which looked at home blood glucose monitoring in non-insulin dependent diabetics treated with standard therapy - gliclazide. The study, similar in design to the study in question, confirmed the role of home glucose monitoring in this patient group. This was naturally the sort of outcome Servier hoped and expected for its blood pressure automeasurement study. Furthermore, the subject of the study was in line with research conducted over the last few years by Servier looking at 24 hour blood pressure control, as assessed by both ambulatory blood pressure monitoring and clinic measurements.

The scientific credibility of the study was in Servier's view further confirmed by both the number of ethics committees that had approved the study (bearing in mind the 1991 Department of Health Guidelines on Ethics Committees that expressly instructed them to consider not only patient safety but also the "scientific merit" of any study) and also the conduct of the study which had been conducted according to good clinical practice.

Turning to the question of the use of standard therapy, Servier said the Authority had stated that:

"The Panel had difficulty in accepting that standardised treatment was necessary for the study which was concerned not with the merits of any particular preparation but with comparison of blood pressure measurements taken in the surgery with those taken by patients themselves in their own homes".

Servier argued that a multiplicity of hypertensive agents with their different treatment regimes and side effect profiles would exert a profound influence on the accuracy and effectiveness of this type of study. Interpretation of both the blood pressure results themselves and the acceptability of automeasurement to both patient and doctor alike would be difficult with so many possible treatment variables. Furthermore, it should be stressed once again that as in the above mentioned paper by Shaw *et al*, no patient receiving clinically effective and acceptable treatment would be included in the study, ie they would not be switched from such a treatment to perindopril simply to be included in the study. Therefore in Servier's opinion this study could not be construed as a "marketing" study.

Practically, Servier felt that in order to reduce the treatment variables to a minimum it should choose a drug which could be administered on a once daily basis, with minimal side effects and able to be used in the majority of patients. Discussion with the late Dr Raftery, its study coordinator, led to the choice of an ACE inhibitor as the principal treatment mode with a once daily diuretic to be added when further control was required. It might also be worth mentioning that the provision of standard therapy in company sponsored trials would seem to be the norm rather than the exception. Perusal of the literature revealed many examples of such a policy and the results of those studies were thought scientifically relevant enough to warrant publication in reputable journals ie peer review considered they were not marketing exercises.

The Panel's judgement also made comment on the insurance aspect of this study. Servier was sure that it would not be expected to assume the liabilities of products originating from other companies. This would have been the case if there had been no standard therapy provision.

Having established the scientific rationale for the study and argued the case for standard therapy for principally scientific reasons and secondly practical, why choose perindopril and indapamide?

Servier's criteria for a treatment of choice to make the therapeutic arm of the study as simple as possible included: once daily therapy, effective 24 hour blood pressure control and good patient acceptability in a broad spectrum of patients. As noted above, the principal treatment selected was an ACE inhibitor and as a

company that manufactured an ACE inhibitor which complied totally with Servier's treatment criteria, it considered that it was fully justified in using it. Whilst Servier could have performed this study with another ACE inhibitor, for the practical reasons outlined in Servier's initial response perindopril was chosen.

In summary, Servier respectfully suggested that this was a valid study on the value of automeasurement in the GP patient population and the phenomenon of "white coat" hypertension. The study also reflected Servier's continuing interest and commitment to the field of patient automonitoring. The use of perindopril for the therapeutic element of the study was fully scientifically justified. In addition, those patients whose hypertension was already satisfactorily managed were excluded from recruitment to the study.

APPEAL BOARD RULING

The Appeal Board did not accept Servier's reasoning for standardisation of therapy on perindopril and indapamide. It was true that this avoided adding to the number of variables but there were already a significant number of variables and the study might well be flawed for that reason. There seemed to be no reason why a study could not have been devised which allowed patients to continue to use their existing medications.

The Appeal Board endorsed the Panel's decision that the study amounted to the promotion of Coversyl and Natrilix. The Appeal Board accordingly ruled that there had been breaches of Clauses 10.2 and 18.1 of the Code. Although the level of payments as such would have been appropriate for a valid trial, as a breach of Clause 10.2 had been ruled it followed that the payments were unacceptable.

The appeal accordingly failed.

As far as the consequences of its decision were concerned, the Appeal Board decided that the recruitment of new doctors and new patients to the study would both have to cease but existing patients could continue to completion. Servier would be required to notify the decision to all doctors involved in the study and all ethics committees which had given approval to the study.

Complaint received **3 July 1995**

Case completed **4 December 1995**

CASES AUTH/318/7/95, AUTH/321/7/95 & AUTH/322/7/95

HOSPITAL PERSONNEL v KNOLL

Conduct of a representative - various allegations

Three complaints were made about the conduct of a representative, it being alleged that she had repeatedly visited a hospital causing inconvenience, that she had falsified an expense claim for dinner at the Ritz by listing doctors who had not been present and that she had made unacceptable allegations about the behaviour of certain doctors to her.

The Panel considered the three complaints together and ruled that the representative had not maintained a high standard of ethical conduct. The Panel also ruled a breach of Clause 2 in view of the serious nature of the events which brought discredit upon and reduced confidence in the industry. It also decided to report the company to the Code of Practice Appeal Board.

The Panel's rulings were appealed and the Appeal Board decided that the hospital visits alleged to cause inconvenience and the unacceptable allegations made by the representative about certain doctors did not come within the scope of the Code. The Appeal Board upheld the Panel's ruling in relation to the excessive hospitality, falsfication of expenses and ruling of Clause 2.

In relation to the Panel's report, the Appeal Board decided not to report the matter onto the ABPI Board of Management in view of assurances that steps were being taken to put the company's procedures in order. It strongly recommended that the company have its procedures audited by the Prescription Medicines Code of Practice Authority.

COMPLAINTS

Case AUTH/318/7/95

A doctor and another member of a hospital's staff complained about the conduct of a representative of Knoll Limited alleging that she had repeatedly interrupted their work by attending at their laboratories despite requests to the contrary. She had often arrived between 10 and 11am and had eventually departed between 4 and 5pm, sometimes even after office hours.

A letter to the local Knoll regional manager amplified the allegations which had been made. The laboratory protocol had been repeatedly flouted. Safety and research regulations did not permit her unsupervised and unscheduled entries into the laboratory during office hours. She arrived unexpectedly without appointment, which was the usual requirement, and became insistent on seeing one of the hospital's doctors despite assertions that he did not wish to be disturbed. On other occasions she had made multiple phone calls to the laboratory trying to contact that doctor even when she was assured that he was not available and her messages had been taken.

RESPONSE

Knoll said that:

1 the representative did not at the relevant time, nor did

she ever have, any professional responsibilities for promoting Knoll products at the hospital in question;

2 it understood that its representative's presence at the hospital was an attempt to resolve a purely personal matter;

3 it further understood that this personal matter had now been resolved and that she had not visited the hospital since June.

Although the incident did not arise out of the performance of her professional duties for Knoll, it submitted that it had taken appropriate disciplinary action. In addition, Knoll considered that it had given the complainants all possible reassurances about the matter. The delay in response referred to by the complainants might well have been caused by the fact that they chose to make their complaint to the Knoll representative responsible for the hospital with specific instructions to pass the letter on to his regional manager. Unfortunately he had no direct responsibility for the representative in question.

In a further response, Knoll said that the personal matter referred to its initial response culminated in the representative being granted an *ex parte* injunction against a member of the hospital's staff. Cross undertakings in a similar form were given a week after the injunction was granted. The complaints which had been received appeared to have been made in the weeks immediately following the hearings.

Case AUTH/321/7/95

An anonymous junior doctor at a hospital said that he had had an unusual telephone conversation with a Knoll representative. This was the same representative as in Case AUTH/318/7/95. The complainant was concerned by her request that "If an enquiry is made, could I confirm that I was at supper with her at the Ritz Hotel, London, recently". The complainant had never been to supper with the representative and questioned her motives and ethics. Moreover the representative asked if the complainant could ask a colleague to do likewise. The complainant alleged that this was not appropriate or acceptable behaviour.

RESPONSE

Knoll said that the representative admitted that she entertained three doctors at the Ritz. The allegation that she incited the complainant to say that he had attended (in order to give the impression of a more modest cost per head) was denied but she admitted to being persuaded to falsify her expense claim.

Case AUTH/322/7/95

A hospital doctor said that he had been surprised to hear from medical colleagues at other hospitals that certain casually dropped allegations about his conduct had been made to them by a Knoll representative. This was the same representative as in Cases AUTH/318/7/95 and AUTH/321/7/95. The suggestion was apparently made by her that, although she could not put her finger on anything specific, the complainant's behaviour to her was in some way inappropriate and amounted to a form of sexual propositioning.

This kind of statement was as impossible to disprove as it was to prove and it was therefore particularly pernicious. The information was of course hearsay but its solidity was strengthened by the fact that a similar allegation was made about a senior colleague at another hospital by the representative to the complainant himself a few months ago. This doctor, who the complainant knew professionally but not really socially, was supposed to have tried to forcibly hug and kiss the representative at the end of a private discussion about Knoll's products. At the time the complainant admitted that he found the story rather amusing but in retrospect it appeared to fit with a behaviour pattern of spreading indiscriminate slanderous gossip about rather senior middle-grade medical staff at a particularly vulnerable point in their careers.

RESPONSE

Knoll said that the representative stated that the remarks made about the complainant were part of a private conversation between her and her partner. The representative stressed that she had not discussed these matters with anybody else.

* * * * * * *

In conclusion, Knoll said that Cases AUTH/318/7/95 and AUTH/322/7/95 arose out of an extraordinary and serious personal issue unrelated to its representative's professional responsibilities. As to Case AUTH/321/7/95, the representative readily acknowledged that the level of hospitality was inappropriate and that it was unfortunate that she had misguidedly falsified an expense claim.

PANEL RULING

Cases AUTH/318/7/95, AUTH/321/7/95 & AUTH/322/7/95

The Panel had some difficulty in assessing which elements of the representative's conduct should properly be regarded as having taken place in the course of her duties as a medical representative and which should not. Some of them had taken place at a hospital for which she was not personally responsible. Nonetheless her activities had annoyed a number of people who had regarded her as being present in her capacity as a Knoll representative. It might well be that Knoll should have taken action at an earlier stage to thoroughly investigate the matter as it had received a letter before the complaint was made to the Authority. As far as the hospitality at the Ritz Hotel was concerned, it was admitted that the level of hospitality had been inappropriate and the representative had falsified an expense claim.

The Panel considered that it was impractical to analyse the individual elements of the representative's conduct with a view to making specific rulings but her conduct had clearly been unacceptable. The Code had certainly been breached, for example, in relation to the hospitality at the Ritz Hotel and the subsequent falsification of expenses and by the inconvenience caused by her calls.

It was the view of the Panel that the representative had not maintained a high standard of ethical conduct in the discharge of her duties and a breach of Clause 15.2 was ruled. In view of the serious nature of the series of events,

a breach of Clause 2 was also ruled. It was also decided to report the matter to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

APPEAL BY KNOLL

Case AUTH/318/7/95

Knoll said that it could not accept that either Clause 2 or Clause 15.2 was applicable. Clause 2 stated that "methods of promotion" must not bring discredit upon the pharmaceutical industry. Its representative's presence at the hospital in question was totally unrelated to her promotional responsibilities for the company and as such it was difficult to see how her conduct could possibly be regarded as a "method of promotion". Clause 15.2 required a high standard of ethical conduct by representatives in the "discharge of their duties". Knoll again could not accept that its representative's attempts to resolve her personal problems with a member of staff at the hospital could be considered as part of her duties. The representative had assured Knoll that she had stressed at the time to all concerned that her presence at the hospital was unrelated to her professional duties for the company.

Knoll submitted a detailed statement as to the background to the incidents at the hospital which involved the relationship between its representative and one of the hospital's doctors. This information had not been made available to the Panel in the first instance because of the unusual nature of the circumstances. Also provided by Knoll was a copy of an injunction obtained by the representative against the doctor at the hospital together with the associated affidavit by the representative, her statement of claim and the undertaking given by the doctor.

Case AUTH/321/7/95

Knoll acknowledged that the level of entertainment was inappropriate but considered that Clause 15.3 was the appropriate provision. The representative asserted that one of the doctors had persuaded her to take him and two of his colleagues for dinner at the Ritz. Given the bill of £250 and in order to reduce the cost *per capita* so as to allay concern on the part of Knoll, it was suggested by one of the diners that the names of two other doctors be added to the meeting report as fictional diners.

Approval had been given by the company for a meeting relating to the promotion of Securon SR on the basis of cost, the expected number of attendees and that it involved doctors from the representative's own territory.

Case AUTH/322/7/95

Knoll said that the representative asserted that her remarks concerning the complainant had been uttered on one occasion only, viz in the course of an informal domestic conversation with her partner.

APPEAL BOARD RULING

The Appeal Board accepted the Chairman's recommendation that, notwithstanding the fact that the Panel had taken the cases together for the purposes of its ruling, it would be appropriate for the Appeal Board to consider them separately as different considerations might well apply in each. The Appeal Board noted, however, that the cases were all interrelated.

Case AUTH/318/7/95

The Appeal Board noted that Clause 2 referred to "methods of promotion" and that Clause 15.2 referred to the maintainance by medical representatives of a high standard of ethical conduct "in the discharge of their duties". Clause 15.9, which was also relevant, stated that "Companies are responsible for the activities of their representatives if these are within the scope of their employment even if they are acting contrary to the instructions which they have been given".

Having reviewed the entirety of the circumstances in this unusual case, the Appeal Board decided that they were to be regarded as being outside the scope of the Code. Notwithstanding the unfortunate impression given to the complainants, the events had taken place at a hospital for which the representative was not responsible and they seemed to reflect the extreme nature of her personal circumstances rather than the mode in which she promoted medicines. The events had not been "methods of promotion" and nor had they occurred in the discharge of the representative's duties or been within the scope of her employment. There was no evidence on which a ruling under the Code could be based. The Code could not be regarded as being applicable. The appeal on this particular aspect therefore succeeded.

Case AUTH/321/7/95

The Appeal Board considered that the dinner at the Ritz was clearly of a promotional nature. Approval for it had been given by the company on the basis that it was promotional. Quite apart from the unacceptable level of hospitality, the falsification of the reporting of the meeting was a serious matter. The Appeal Board did not accept Knoll's submission that there had merely been a breach of Clause 15.3 and ruled that there had been breaches of Clauses 2 and 15.2 of the Code. The appeal on this particular aspect therefore failed.

Case AUTH/322/7/95

The Appeal Board decided that the circumstances of this case were similar to those in Case AUTH/318/7/95, in that they seemed to reflect the representative's private life rather than her professional duties. There was no evidence on which a ruling under the Code could be based. The Code could not be regarded as being applicable. The appeal on this particular aspect therefore succeeded.

REPORT FROM THE CODE OF PRACTICE PANEL

The Appeal Board was then invited to consider the report from the Code of Practice Panel made under Paragraph 8.2 of the Constitution and Procedure. The Appeal Board noted that Paragraph 8.2 stated that "The Code of Practice Panel may also report to the Appeal Board any company whose conduct in relation to the Code, or in relation to a particular case before it, merits consideration by the

Appeal Board in relation to the provisions of Paragraph 10.3 and 11.1 below".

Paragraph 11.1, which was the relevant provision in the circumstances, stated that "Where the Code of Practice Appeal Board considers that the conduct of a company in relation to the Code or a particular case before it warrants such action, it may report the company to the Board of Management of the ABPI for it to consider whether further sanctions should be applied against that company". The Chairman outlined the sanctions set out in Paragraph 11.2 which were available to the ABPI Board in such circumstances.

APPEAL BOARD DECISION

The Appeal Board had a number of concerns about the events. It had reservations on the question of whether the company had taken matters in hand firmly and quickly enough. Even though there was no evidence that certain of the events came within the scope of the Code, they clearly merited the immediate attention of the company. The falsification of a meeting report to make it appear that the expenses involved were acceptable was particularly serious but did not appear to have been taken seriously enough by the company. Except for an earlier precautionary period of one week, the representative had not been suspended until September and then only as a result of the Panel's rulings.

The Appeal Board noted that the company had been involved in a merger and reorganisation and considered that it needed to take steps as a matter of urgency to ensure that its conduct as regards promotion and the Code was in order. The Appeal Board noted that the company's general manager was new to the post and accepted his assurances that he would be taking appropriate steps. In view of this, and the fact that the events involved the activities of a single medical representative, the Appeal Board decided not to report the matter on to the ABPI Board. It made a strong recommendation, however, that Knoll ask the Prescription Medicines Code of Practice Authority to audit its procedures for complying with the Code.

Complaints received	
Case AUTH/318/7/95	**11 July 1995**
Case AUTH/321/7/95	**21 July 1995**
Case AUTH/322/7/95	**24 July 1995**
Cases completed	
Case AUTH/318/7/95	**18 October 1995**
Case AUTH/321/7/95	**6 November 1995**
Case AUTH/322/7/95	**18 October 1995**

CASE AUTH/324/8/95

CIBA v SOLVAY

Fematrix detail aid

Ciba complained about a detail aid for Fematrix issued by Solvay. There were six allegations in total.

Four allegations ruled in breach of the Code by the Panel were subsequently appealed by Solvay to the Appeal Board which upheld the Panel's rulings. These were firstly a graph which was ruled to be misleading as dotted lines were included in the graph during the time period when no samples were taken. It was considered that the dotted lines might be taken by readers to be an indication of the expected results and this was not so. Secondly, a claim "Non-irritant in eczema-prone patients" was ruled not to be adequately substantiated by clinical experience. Thirdly a bar chart was ruled to be visually misleading as it conveyed an impression that there was a large difference between the products although the difference was not statistically significant. Fourthly claims "superior sweat cooling" and "superior sticking" were ruled to be hanging comparisons in breach of the Code.

Two allegations were ruled by the Panel not to be in breach of the Code. Firstly, an allegation that there was no evidence to justify a claim that Fematrix should be considered as a first line treatment was not accepted by the Panel as the product could be used as a first line option. Secondly, an allegation that the general style and tone of the booklet did not recognise the professional standing of the audience nor the special nature of medicines was not accepted.

Ciba Pharmaceuticals complained about a detail aid for Fematrix (Fex/01/Mar/95) issued by Solvay Healthcare Ltd. There were six allegations which were considered was as follows:-

1 Graph showing oestradiol plasma concentration time profiles of Fematrix and a 50mg reservoir patch.

The graph compared the oestradiol plasma concentration of Fematrix and a reservoir patch over a period of 16 days. The time periods between days 1 and 4 and days 8 and 11 were coloured grey with an explanatory statement "no samples taken". When samples were taken solid lines were shown on the graph and during the time periods when no samples were taken dotted lines were used to join the solid lines together to make a line for each product. The graph for Fematrix was a steadier line than that for the reservoir patch which showed distinct peaks and troughs.

COMPLAINT

Ciba Pharmaceuticals alleged that the results presented in the graph were misleading in that only limited blood level measurements of oestradiol for Fematrix and its own patch Estraderm, shown as the reservoir patch in the graph, had been carried out and presented. The graph

suggested to the uninitiated that during days 1 to 4 and 8 to 11 when no samples were taken, oestradiol blood levels from Estraderm were way below those of Fematrix. The reality was of course that an Estraderm blood level profile similar to that seen during days 4 - 8 and 11 - 14 was occurring during these times making any difference between the products much less than was apparent. A breach of Clause 7.2 of the Code was alleged as the graph did not provide a balanced view.

RESPONSE

Solvay Healthcare Ltd submitted that the graph was taken from a pharmacokinetic comparison of Fematrix and Estraderm and was clearly labelled with grey shaded areas to indicate the time intervals during which no samples were taken. The lines through these shaded areas were broken to distinguish them from the continuous lines as represented by the mean plasma levels achieved during the sampling periods.

The graph was included to demonstrate the differences in the pattern of plasma oestradiol level delivery between Fematrix and Estraderm. The graph clearly demonstrated that smooth and sustained oestradiol levels were achieved following the application of Fematrix during the sampling period compared with the peaks and troughs achieved with Estraderm during the same periods. The company submitted that the distinction between actual levels achieved and non sampling periods had been made clearly and it would expect any reader to compare levels only where the continuous lines were shown. It was not intended to imply that the broken lines represented actual levels nor that both continuous and broken lines for each product should be compared. It would have been foolish to imply this as to have done so would have misrepresented in a derogatory fashion the actual levels achieved with Fematrix and shown the company to be inconsistent in its message about oestradiol patterns achieved with Estraderm. The point being made was that Estraderm did not deliver oestradiol in a similar smooth and sustained manner to Fematrix.

PANEL RULING

The Panel noted that the graph was labelled to indicate that the shaded grey areas related to days when no samples were taken. It considered, however, that the dotted lines would be taken as estimations of the oestradiol plasma concentrations during that time and this was not so. The dotted line for Estraderm was significantly different to the likely actual values as no account had been taken of the fact that a new patch was applied on days 1 and 8. The Panel ruled that the graph was misleading in breach of Clause 7.6 of the Code.

APPEAL BY SOLVAY

Solvay stated that the purpose of the graph was not to attempt to show overall differences in the magnitude of the plasma concentrations produced by the two patches but rather to show the different patterns of oestrogen delivery. This should be clear from the context of the graph appearing on a page headed "Ensuring smooth delivery" and for the bold large print claim on the opposite page "Smooth - releasing, menopause easing new Fematrix".

The message given related to the smooth release pattern of oestrodial from the matrix patch. There was no attempt to imply that the absolute plasma concentration produced by the two types of patches would result in different therapeutic effects. The graph was very clearly labelled.

APPEAL BOARD RULING

The Appeal Board considered that some readers might assume that the dotted lines on the graph were an indication of the expected results if samples had been taken during the relevant time period and this was not so. The Appeal Board therefore upheld the Panel's ruling that the graph was misleading in breach of Clause 7.6 of the Code.

The appeal therefore failed.

2 Claim "Non-irritant in eczema-prone patients"

COMPLAINT

Ciba said that the claim was based on the findings of a 48 hour Fematrix/placebo application in 50 eczema prone volunteers. The relevance of the findings of the study to long term clinical use with Fematrix could only be conjectural and did not support the absolute statement made. A breach of Clause 7.7 of the Code was alleged.

RESPONSE

Solvay submitted that the claim accurately reflected the result of the clinical study cited, namely that Fematrix was shown to cause no irritancy in eczema prone patients. The study was designed to assess the irritancy potential of Fematrix using primary irritancy patch testing, a skin testing system designed to detect substances with a potential to cause irritation or dermatitis. This was achieved by means of a single 48 hour period of occlusive application. The testing was carried out in eczema prone subjects to increase the sensitivity of the test system. It was widely accepted by dermatologists that if a substance was non irritant in this group of subjects it could be presumed to be non irritant under normal conditions in the general population.

Solvay submitted that the assessment of Fematrix using the testing procedure would be generally accepted to indicate that the product had a low, if any, irritancy potential with repeated and longer term use.

PANEL RULING

The Panel noted that the study had been carried out on 50 eczema prone volunteers, 25 male, 25 female, and that no irritation had been recorded in any volunteer 48 hours after the patch was removed. One volunteer demonstrated mild erythema to both Fematrix and placebo but this volunteer had been found to be allergic to nickel, ammonia persulphate and glycerol monothioglycolate. The study concluded that Fematrix exhibited an extremely low irritancy potential.

Although the study gave some support the Panel

considered that it was not sufficient to support such a strong claim as "non-irritant in eczema-prone patients" which would be taken as a general comment relating to longer term use. A breach of Clause 7.7 of the Code was ruled as the claim referred to a side effect and had not been adequately substantiated.

APPEAL BY SOLVAY

Solvay submitted that the basis of the claim was a specific clinical trial, but in addition the overall clinical experience with Fematrix was relevant. This was an accurate reflection of experience with Fematrix and available data provided justification for what was a reasonable statement. The company did accept that no claim could be considered to be guaranteed for all time as there were too many precedents showing otherwise.

Solvay pointed out that the study in eczema prone patients was a primary irritancy patch test which was a well established method. If non irritant in sensitive patients a product was considered to be non irritant in the general population. The study investigator had concluded "no irritant reaction" and not as the Panel had noted "extremely low irritancy potential".

Solvay drew attention to a claim "Minimal redness/irritation" which referred to the results of a study in 200 patients and appeared immediately beneath the disputed claim. In the study some patients had experienced redness.

APPEAL BOARD RULING

The Appeal Board noted that the study in question stated in the results section that no irritation had been recorded in any subject. The study concluded that Fematrix exhibited an extremely low irritancy potential.

The Appeal Board considered that the claim was not sufficiently qualified given that it appeared immediately above a claim "minimal redness/irritation" and data showing that 3% of patients on Fematrix had well defined erythema 30 minutes after removing the patch. The disputed claim was not supported by clinical experience.

The Appeal Board therefore upheld the Panel's ruling that the claim was in breach of Clause 7.7 of the Code as it referred to a side effect and had not been adequately substantiated.

The appeal therefore failed.

3 Bar chart headed "Draize-scale assessment: percentage of patients with well-defined erythema (30 minutes post removal)

The bar chart gave figures of 12% for the reservoir patch and 3% for Fematrix above the relevant bars. Immediately adjacent to the figure 3% was an asterix which was explained immediately below the label for the Fematrix bar as meaning not statistically significant. The bar chart appeared beneath a claim "Minimal redness/irritation".

COMPLAINT

Ciba alleged that there was no scale to the bar chart which exaggerated a non significant difference between the two products in breach of Clause 7.6 of the Code.

RESPONSE

Solvay said that the scale to the bar chart was implied by the value assigned to the bars. It considered that they were adequately labelled such that the bar chart could be clearly understood and not considered misleading.

PANEL RULING

The Panel did not accept that there was a need for a scale on the bar chart as the values were given at the top of each bar. The Panel considered, however, that despite the labelling the bar charts were visually misleading as they conveyed the impression that there was a large difference between the products although this difference was in fact not statistically significant. The Panel therefore ruled a breach of Clause 7.6 of the Code.

APPEAL BY SOLVAY

Solvay submitted that the bars were clearly marked to show that the difference was not statistically significant. Furthermore there was no claim relating to superiority. Whilst there was a difference in bar height this was not large and 9% was unlikely to be of clinical relevance. The company did not think that this would be misleading in view of the indicated lack of statistical significance and the overall clarity of the chart.

APPEAL BOARD RULING

The Appeal Board considered that the bar chart was visually misleading as it conveyed the impression that there was a large difference between the products although this difference was not statistically significant.

The Appeal Board therefore upheld the Panel's ruling that the bar chart was misleading in breach of Clause 7.6 of the Code.

The appeal therefore failed.

4 Claim "Cost aware, first line care"

COMPLAINT

Ciba alleged that the claim was in breach of Clause 7.8 as there was no evidence to justify the claim that the product should be considered as a first line treatment.

RESPONSE

Solvay pointed out that the product licence for Fematrix stated that it was indicated for the treatment of symptoms of oestrogen deficiency as a result of a natural menopause or oophorectomy. There were no restrictions/conditions on the licence to indicate that it should not be considered a first line treatment option for this indication. The company submitted that under Clause 7.4 of the Code substantiation for any claim need not be provided in relation to validity of indications approved in the marketing authorisation.

RULING

The Panel considered that the claim was not stating that Fematrix was the only treatment and nor was it stating that it was the first line treatment. The Panel accepted the submission from the company that Fematrix could be used as a first line treatment option. The Panel therefore ruled no breach of the Code.

5 Claims "Superior sweat cooling" and "Superior sticking"

COMPLAINT

Ciba alleged that the claims were hanging comparisons in breach of Clause 7.2 of the Code.

RESPONSE

Solvay pointed out that the claims appeared as part of a list of bullet points on the back page of the piece summarising the information within. Each had been referenced. It was quite clear from the booklet as to what the comparative treatment was and it did not agree that the statements could be regarded as a hanging comparison.

PANEL RULING

The Panel noted that the claims appeared on the back page of the booklet and that there was no mention of the reservoir patch on this page. The Panel had some sympathy with the submission from Solvay that it was clear from the booklet as to what was the comparative treatment. The Panel considered, however, that context was an important factor. The claims appeared on the back page of the booklet which might well be read before the inside pages. It was not clear from the page in question what was being compared to Fematrix. The Panel therefore ruled that the claims were hanging comparisons in breach of Clause 7.2 of the Code.

APPEAL BY SOLVAY

Solvay submitted that the page upon which the claims appeared was merely a summary of the main points in the detail aid together with prescribing information. It would be apparent even to a casual back page reader that the full detail aid should be read if details of any of the bulleted claims were required. Solvay agreed that context could be an important consideration in assessing clarity or otherwise of promotional items but even so it did not feel that the detail aid was misleading in respect to claims made or that the claims should be considered as "hanging".

Solvay reiterated that the material was a detail aid and would be discussed with the doctor by a medical representative. The back page was to reinforce the points made in the booklet itself.

APPEAL BOARD RULING

The Appeal Board noted that the supplementary information to Clause 7.2 stated that hanging comparisons whereby a medicine was described as being better or stronger or suchlike without stating that with which the medicine was compared must not be made. The Appeal Board had some sympathy with the submission from Solvay that it was clear from the full text of the detail aid as to what the comparative treatment was and that the detail aid was to be used with doctors during an interview with a medical representative. The Appeal Board nonetheless considered, however, that it was not clear from the page in question as to what was the comparative treatment.

The Appeal Board therefore upheld the Panel's ruling that the claims were hanging comparisons in breach of Clause 7.2 of the Code.

The appeal therefore failed.

6 General style and tone of the booklet

COMPLAINT

Ciba alleged that the booklet trivialised the menopause and hormonal loss in hysterectomised women and undermined the standing of the pharmaceutical industry. It alleged that statements such as "menopause easing", "flush soothing, sweat cooling", "skin aware" and "slick fitting" did not recognise the professional standing of the audience nor special nature of medicines. A breach of Clause 9.1 was alleged.

RESPONSE

Solvay submitted that the booklet had been carefully and thoughfully created with usual consideration for the professional standing of the audience to which it was directed. It was well established and accepted that hormone replacement therapy could have significant impact on a woman's quality of life and sense of well being and it had endeavoured to reflect this in the tone of the booklet. Before finalising the booklet it researched both the visuals and the text with a number of general practitioners for their opinion. Overall the reaction was most positive, the majority commenting on its impact and how well it reflected the potential benefits of HRT. The company had received no negative feedback nor any comments to suggest that the doctors felt that the tone was unsuitable nor that it trivialised the menopause. A copy of the research was provided.

With regard to the statements "Menopause easing", "flush soothing, sweat cooling", "skin aware" and "slick fitting" the company submitted that each was clear, accurate, objective and could be substantiated.

RULING

The Panel appreciated that taste was subjective matter. It considered that the booklet was not unacceptable with regard to the requirements that promotion should recognise the special nature of medicines and the professional standing of the audience. The Panel therefore ruled no breach of Clause 9.1 of the Code.

Complaint received 9 August 1995

Case completed 3 November 1995

CASE AUTH/332/9/95

PFIZER v KNOLL

Securon SR cost comparison chart

Pfizer complained that a cost comparison chart in a Securon SR leavepiece produced by Knoll was misleading as it gave the usual maintenance dose of Pfizer's product amlodipine in the treatment of hypertension as 10mg daily. The recommended dosage of amlodipine in the data sheet was given as 5mg once daily which might be increased to 10mg daily depending on the individual patient's response.

The Panel considered that given the ambiguity of the term "usual adult maintenance dose" used in the chart and the data it was misleading to state that the usual adult maintenance dose of amlodipine was 10mg. Knoll had failed to take account of all the available data and a breach was ruled. In the Panel's view it would also have been unacceptable to say that the usual maintenance dose was 5mg.

Pfizer Limited submitted a complaint regarding a cost comparison chart in a Securon SR leavepiece.

The cost comparison chart was headed "Comparative costs of one-a-day calcium antagonists for hypertension" and compared the cost of Securon SR, verapamil SR capsules, nifedipine LA, amlodipine (Pfizer's product, Istin), lacidipine and diltiazem LA. There were two columns, one headed "Lowest dose cost per 28 days £" and the second "Usual adult maintenance dose - cost per 28 days £". The doses of nifedipine LA and amlodipine were given in brackets next to the costs.

COMPLAINT

Pfizer alleged that by stating that the usual maintenance dose of amlodipine in the treatment of hypertension was 10mg daily, the chart was incorrect and misleading in breach of Clause 7.2 of the Code. The company pointed out that the recommended dosage of amlodipine in the treatment of hypertension given in the data sheet was "5mg once daily which may be increased to a maximum of 10mg daily depending on the individual patient's response".

Pfizer stated that most patients treated for hypertension were controlled on 5mg daily and this was supported by several large studies in the treatment of hypertension. The company referred to a large UK study in general practice (Cross *et al*) which showed that 64.2% of patients were controlled on 5mg amlodipine daily. The US treatment of mild hypertension study (TOMHS) included 902 patients of whom 131 received amlodipine. This study was particularly important as patients were followed for four years. At the end of the study 82.5% of patients were controlled on amlodipine 5mg; the highest proportion of the four medicines included to be controlled on the initial dosage. A study by Omvik *et al* included 231 patients treated with amlodipine for one year and reported that 55% of patients were maintained on amlodipine 5mg daily. An international study of amlodipine in general medical practice (Varonne *et al*) included 320 patients and showed that 63% of patients were controlled on amlodipine 5mg.

Pfizer said that 5mg as the usual daily dosage of amlodipine to treat hypertension was further substantiated by audited data from IMS and DIN-LINK. The IMS audit, the Medical Data Index (MDI), showed that 60% of all amlodipine prescriptions were for 5mg daily. The DIN-LINK (ex compufile, MAT June 1995) showed that in hypertension 65% of amlodipine prescriptions were for 5mg daily. In angina, 66% of amlodipine prescriptions were for 5mg daily.

Pfizer considered that the response it had received from Knoll to justify its use of amlodipine 10mg as the usual daily dosage, citing a number of small studies which were specialised by objective and design, could not be used to derive the usual dose of amlodipine in routine clinical practice. Detailed criticisms of Knoll's points were provided.

RESPONSE

Knoll Pharma Ltd pointed out that the chart compared the cost of once a day calcium antagonists at what were described as "lowest" and "usual" doses per day. In order that there could be no misunderstanding by the doctor, the daily costs of amlodipine were clearly given by dose, 5mg and 10mg, as well as by the descriptors of "lowest" and "usual". This allowed the doctor to make the comparison relevant for individual patients needs.

Knoll submitted that the choice of what constituted the usual dose was arrived at from a review of what were considered to be relevant studies conducted with adequate control and good methodology. Knoll made a number of criticisms of the studies supplied by Pfizer to support the allegation. With regard to the study by Cross *et al*, Knoll said that it could only produce useful information on the safety and tolerability of amlodipine as indicated by the tone of the paper. The open nature of study design severely limited its ability to provide information on what was the most effective or optimum dose of the product.

In the US TOMHS study, the patients entering the study had a mean diastolic blood pressure of 90.9 mmHg, a level that one would consider borderline in considering treatment. For those patients not on therapy, the lowest pressure allowed was 90 mmHg and for those withdrawn it was 85mmHg. It did not seem surprising that the dose of amlodipine required in this population was only 5mg. In addition, the measurements were taken one to four hours after the dose at what one might reasonably consider to be around the peak effect, not at the end of the dosing interval which was arguably the more relevant measurement.

The study by Omvik *et al* neither supported or refuted either of the conntentions on the usual dose as the proportion of patients in each dose group were evenly divided 55% on 5mg and 45% on 10mg.

Knoll submitted a number of studies to support its view that the usual maintenance dose of amlodipine was 10mg daily.

In a placebo controlled dose finding study by Frick *et al*, 78% of patients initially started on 5mg daily required upward titration to 10mg daily. A study by Lorimer *et al*, compared amlodipine with verapamil and 93% of patients on amlodipine required dose titration to 10mg daily. Knoll acknowledged that this study was criticised by Pfizer on the grounds that the dose titration of amlodipine was too rapid. This seemed strange to Knoll as the study was reported with a Pfizer employee as one of the study collaborators in the study. Heber *et al* in a 24 hour blood pressure study showed that 8 out of 14 patients (57%) required dose titration from 5mg to 10mg daily. Webster *et al*, using tolerability criteria, showed that 13 patients out of 15 patients (87%) required dose titration to 10mg daily.

In a double blind comparative study versus atenolol (Johnson *et al*), 41 patients randomised to amlodipine received a mean daily dose of 8.8mg indicating that more patients were on 10mg daily than the other lower daily doses. Engbert *et al* in a study comparing amlodipine with nitrendipine found that the mean daily dose of amlodipine was 8.4mg, again indicating that the majority of patients were titrated to 10mg daily. Similarly, in a study by Rofman *et al*, only 37 out of 92 patients (40%) had adequate blood pressure control after 50 weeks treatment with amlodipine (up to 10mg daily) alone, the remainder required the addition of atenolol.

In a long term double blind study (Ram *et al*) comparing amlodipine with hydrochlorothiazide only 26% of patients randomised to amlodipine (up to 10mg per day) attained blood pressure control after 26 weeks of treatment in marked contradiction to the response rate of 61.5% after 12 weeks of treatment. What was even more revealing was that 53 out of 97 patients (55%) randomised to amlodipine treatment required the addition of atenolol after reaching the maximum dose of amlodipine 10mg daily. These studies using a free dose titration regimen based on blood pressure response and tolerability indicated that a significant proportion of patients required the maximum dose of amlodipine ie 10mg daily allowed by protocol.

Knoll submitted that using both efficacy and tolerability criteria, the properly designed placebo and active comparator studies of amlodipine in mild to moderate essential hypertension did not substantiate the argument that 5mg daily was the correct or optimum maintenance dose of amlodipine. On the contrary, 10mg daily would appear to be the scientifically proven useful adult maintenance dose of amlodipine.

RULING

The Panel noted that the chart gave the doses of amlodipine and nifedipine upon which the costs were calculated.

The Panel examined the data provided by Pfizer to support its view that the usual daily dose of amlodipine was 5mg.

It was not clear to the Panel whether the IMS audit and the MDI data that 60% of all amlodipine prescriptions were for 5mg daily related to its use in hypertension only (the subject of the chart) or to its use in the treatment of both hypertension and angina.

The Panel noted that the Cross *et al* study in general practice in the UK was primarily a safety study of 10 weeks' duration. It was open and non-comparative with some patients continuing with existing antihypertensive therapy and others not. It appeared to be not possible from the data provided to work out exactly the numbers on each treatment regimen and the outcome. The mean final daily dose of amlodipine in the study was 6.8 mg with two thirds of patients maintained on a daily dose of 5 mg.

The Panel accepted Knoll's view of the TOMHS study that it was not surprising that the dose of amlodipine required in the population studied was 5mg daily. In this regard, the Panel noted that patients entering the study had a mean diastolic blood pressure of 90.9mmHg which would be borderline in considering treatment. Further that for the patients not on therapy, the lowest pressure allowed was 90mmHg and for those withdrawn from their antihypertensive medicines before commencing the study, the lowest pressure allowed was 85mmHg.

The Panel noted that in the Omvik study, a multi centre double blind comparative study, patients entering the study had an average diastolic blood pressure of 106 mmHg. The mean final visit dose of amlodipine was 7.2mg per day with 128 (55%) patients maintained at the end of the trial on a daily dose of 5mg and 103 (45%) maintained on a daily dose of 10mg.

The Panel noted that the Varrone *et al* study, an open multi centre GP study on the efficacy and safety of amlodipine provided by Pfizer, was an interim analysis of data from 320 patients. The Panel noted that Pfizer's view was that the study showed that 63% of the 320 patients were controlled on amlodipine 5mg. It appeared to the Panel that the figure of 62.8% from the study referred to the number of therapy successes in the amlodipine monotherapy group (175 patients out of 194) controlled on 5mg daily (110 patients). The position was not quite as described in the complaint.

The Panel examined the evidence provided by Knoll to support its view that the usual daily dose of amlodipine was 10mg. The Panel noted that some of the studies had been carried out on small numbers of patients and in some studies it seemed that it was not possible to ascertain the number of patients on each regimen. It considered that the studies did give some support to Knoll's view but Knoll had failed to take account of the studies cited by Pfizer.

It appeared to the Panel that Pfizer and Knoll had used conflicting definitions of the term "usual adult maintenance dose". Pfizer considered that the usual dose referred to the most frequently prescribed dose whereas Knoll had taken it to mean the correct or optimal dose.

The Panel considered that the term "usual adult maintenance dose" was ambiguous when used to describe amlodipine given that two different doses were commonly used. There was no information in the data sheet as to what was the usual adult maintenance dose. The Panel accepted that there was some evidence to show that the most frequently prescribed dose was 5mg daily. The Panel considered that given the ambiguity of the term

"usual adult maintenance dose" and the data it was misleading to state that the usual adult maintenance dose was 10mg. Knoll had failed to take account of all the available data. A breach of Clause 7.2 was ruled. In the Panel's view however, it would also have been unacceptable to state that the usual adult maintenance daily dose was 5mg.

Complaint received 12 September 1995

Case completed 31 October 1995

CASE AUTH/333/9/95

GENERAL PRACTITIONER v MEMBER COMPANY

Patient information leaflet

A general practitioner alleged that a patient information leaflet was inappropriate as it referred to a particular effect of a product which was not the licensed indication and patients might want to continue on the product for that effect when the condition for which the product was licensed had resolved.

The Panel considered that the effect needed to be mentioned in the leaflet given its significance. The leaflet was considered to be exempt from the requirements of the Code as it was not promotional.

COMPLAINT

A general practitioner complained about a patient information leaflet issued by a member company for one of its products. The complainant acknowledged that the leaflet had been submitted to the appropriate authority for approval.

The complainant was concerned that the early part of the patient information leaflet referred to a particular effect of the product which was not the licensed indication. Patients might want to continue taking the product for that effect when the condition for which the product was licensed had resolved. The complainant's view was that many general practitioners were unaware that the product was unlicensed for this effect.

RESPONSE

The company submitted that the order in which material was presented within a patient information leaflet was determined by regulations. The order did not denote any degree of importance. The leaflet stood or fell on its total content and individual items should not be considered in isolation.

The company submitted that the separate effect of the product was a well known side effect of the product. It would be negligent not to mention it as there might otherwise be a problem with the co-prescription of other medication with similar properties. The company did not seek to promote the product for this particular effect but it was imperative that the patient be provided with appropriate information.

RULING

The Panel noted that the patient information leaflet would have been approved by the Medicines Control Agency in accordance with the relevant regulations.

The Panel noted that the product was unusual as it had a very specific effect which was quite different to the purpose for which the product was licensed. The Panel considered that this effect was of such significance that it had to be drawn to the attention of patients to avoid the possibility of patients taking other medication with similar effects and to explain a particular consequence of taking it.

The Panel noted that under Clause 1.2 of the Code the labelling on medicines and the accompanying package leaflets insofar as they were not promotional for the medicines concerned were exempt from the Code. The Panel examined the patient information leaflet and decided that it was exempt from the requirements of the Code as it was not promotional for the product. It merely provided information for patients.

Complaint received **8 September 1995**

Case completed **16 October 1995**

CASE AUTH/334/9/95

GENERAL PRACTITIONER v ROCHE

Patient information on malaria

A general practitioner complained that a leaflet on malaria produced by Roche for patients was misleading as information regarding malaria risk referred only to areas where Roche's product Lariam might be used.

The Panel ruled a breach of Clause 20.2 of the Code as the leaflet was not accurate in that the list of countries/regions given under a heading "Malaria - Where are the risks?" was not comprehensive. Countries such as India and Pakistan with a high malaria risk were not mentioned.

The complaint concerned a leaflet headed " Essential advice about malaria for British travellers to tropical countries" (P468066 6/95) produced by Roche Products Limited. The company name was not given on the leaflet.

COMPLAINT

A general practitioner complained that a section in the leaflet detailing areas of malaria risk seemed to refer only to the areas where Lariam (Roche's product) might be used. The complainant alleged that this was misleading to patients and was particularly likely to cause problems in his practice where 37% of patients had the Indian sub-continent as their ethnic origin. A breach of Clause 20 of the Code was alleged.

RESPONSE

Roche Products Limited agreed with the complainant that the leaflet should have included a more comprehensive list of malarious areas. It would not be distributing further copies and had ordered all remaining copies to be destroyed. Any future editions would be suitably comprehensive.

Roche did not however believe that the leaflet was in breach of Clause 20 of the Code as it was not promotional, it did not raise unfounded hopes of successful treatment and nor did it mislead with respect to safety of any medicine.

The company pointed out that there had been important changes to the availability of anti-malarial medicines on NHS prescription. The leaflet thus provided important, factual information which the travelling public and doctors needed to know. Together with a map (provided with the leaflets but not the subject of the complaint) the company believed that it had attempted to provide an appropriate service, the one omission to be corrected in future editions of the leaflet.

RULING

The Panel examined the section of the leaflet the subject of the complaint. It was headed "Malaria - where are the risks?" and a number of countries and regions were listed. Neither India nor Pakistan were included.

The Panel examined the map provided by Roche which appeared on a poster with other information. From the map it appeared that there were a number of countries, such as Pakistan, India and Sri Lanka, which were high malaria risk areas but had not been mentioned in the leaflet. The Panel noted that above the map there was a list of countries together with a recommended anti-malaria regimen for each country. It appeared that the regimen recommended for countries mentioned in the leaflet was mefloquine (Lariam). The Panel noted that the recommended treatment regimen for Pakistan, India and Sri Lanka given in the poster was chloroquine and proguanil with mefloquine as second choice. The poster also included a statement "The regimens have been selected to deal with local patterns of resistance".

The Panel did not accept the submission by Roche that the leaflet was not subject to the Code. The Code covered the provision of non-promotional information to the public. The leaflet referred to medicines in general terms and the Panel therefore considered that it came within the scope of Clause 20 of the Code.

The Panel considered that the leaflet was not accurate as the list of countries/regions given under the heading "Malaria - where are the risks?" was not comprehensive. Readers travelling to high malaria risk countries such as India, Pakistan and Sri Lanka would assume that there was no risk of malaria and this was not so. The Panel therefore ruled a breach of Clause 20.2 of the Code.

The Panel noted that the leaflet had been withdrawn and considered that any future edition of the leaflet should include the company name. It requested that this be drawn to the attention of Roche.

Complaint received 14 September 1995

Case completed 16 October 1995

CASE AUTH/335/9/95

HOSPITAL DOCTOR v KNOLL

Journal advertising for Gopten - misleading claim

The chairman of a hospital drug and therapeutics committee complained about an advertisement for Gopten issued by Knoll which claimed that Gopten protected against stroke and myocardial infarction. The complainant alleged that there was no evidence that any ACE inhibitor protected against stroke and myocardial infarction and no evidence that they did anything to reduce morbidity and mortality in hypertensive patients.

The Panel ruled that the advertisement misled as the evidence showed that only a proportion of those treated would benefit in the way described and also ruled that the claim at issue was a claim for an unlicensed indication.

COMPLAINT

The chairman of a hospital drug and therapeutics committee complained about a journal advertisement for Gopten issued by Knoll Pharma Ltd. The complainant said that the advertisement stated that Gopten protected against stroke and myocardial infarction, even when a dose was omitted. There was no evidence that any ACE inhibitor protected against stroke and myocardial infarction and no evidence that they did anything to reduce morbidity and mortality in hypertensive patients. The advertisement was therefore misleading and should be withdrawn.

RESPONSE

Knoll Pharma Ltd said that the text did not claim a specific action associated with ACE inhibitors. The claim was that by maintaining a lowering of blood pressure over the twenty-four hour period after a missed dose, the protective effect of lowering blood pressure in hypertensive patients was maintained.

The established aim of the treatment of hypertension was to prevent complications and prolong life. High blood pressure *per se* carried with it an increased risk of cardiovascular damage. In a review article by Zannad, reference was made to the fact that reduction in blood pressure for the full twenty-four hour period might result in lower cardiovascular events, mentioning specifically the early morning rise in blood pressure and its association with major cardiovascular and cerebrovascular events. An authoritative review of randomised trials in hypertension (Collins *et al*) indicated that reduction in diastolic blood pressure of only 5mmHg removed at least one third of the risk of stroke and one fifth that of coronary heart disease.

The evidence indicated that lowering blood pressure *per se* reduced the risk of stroke and myocardial infarction. Knoll therefore suggested that its claim that maintaining a lowered more normal blood pressure protected against these events was supportable.

RULING

The Panel noted that Gopten was indicated for mild to moderate hypertension. The claim at issue was "Gopten maintains BP control for up to 48 hours protecting the patient against strokes and M.I.s even when a dose is omitted".

The Panel considered that there were two problems with the claim. Firstly, it misled by implying that all patients were protected against strokes and myocardial infarction even when a dose was omitted, whereas the evidence provided suggested that lowering blood pressure would benefit in this way only a proportion of those treated. Any particular patient would not necessarily be protected.

The second area of concern was whether the claim amounted to a claim that Gopten protected patients against strokes and myocardial infarction which, in the Panel's view, would be a claim for an unlicensed indication given that Gopten was licensed only for mild to moderate hypertension. The Panel accepted that there was evidence that maintaining blood pressure control reduced the risks of strokes and MIs and considered that this would potentially be a feature of therapy with antihypertensives generally. The Panel considered that the claim at issue was more than the reporting of a potential benefit of treatment. It amounted to a claim for an unlicensed indication.

The Panel ruled that there had been breaches of Clauses 3.2 and 7.2 of the Code.

Complaint received **15 September 1995**

Case completed **6 November 1995**

CASE AUTH/337/9/95

HOSPITAL PHARMACIST v MEMBER COMPANY

Conduct of a representative

A hospital pharmacist complained about an interview between a representative from a member company and a pharmacy technician about the use of products. The complainant was concerned about the content of the conversation and the fact that it had been held in the waiting room entrance.

The Panel noted that the Code did not in principle prohibit representatives from talking to pharmacy technicians. The representative had in the past discussed matters in the waiting room entrance. The Panel considered that there was not sufficient evidence upon which a ruling of a breach of the Code could be based. Given the circumstances the Panel ruled no breach of the Code. It would be advisable for the representative to bear in mind the complainant's comments and views in future dealings with the hospitals concerned.

COMPLAINT

A principal hospital pharmacist complained about the conduct of a representative from a member company. The complainant provided a copy of her letter to the company about the matter.

The complainant was disturbed when she visited the pharmacy department to observe that the representative was engaged in conversation with a pharmacy technician about the use of certain of the company's products. It was alleged that during the course of the conversation the representative made critical reference to the judgment of the formulary pharmacist and the contents of the locally agreed prescribing guide. At this point the complainant introduced herself and suggested that some of the statements were not wholly accurate.

In the complainant's view there was no point in the representative conducting this type of conversation with pharmacy technicians. The point of contact should be with the pharmacy business manager, formulary pharmacist, clinical pharmacist etc. The complainant alleged that discussing the formulary pharmacist and the prescribing guide in a public place was unprofessional behaviour on the part of the representative. The complainant stated that her intervention in the conversation did not deflect the representative from her clear goal of complaining about the use or otherwise of the company's products.

RESPONSE

The company concerned submitted that most of its products were listed on the hospital formulary. As the usual pharmacist was away at the eye infirmary for the day, conversation was made with the pharmacy technician on duty and the representative began to introduce the range of products to this individual.

The representative denied making critical reference to the judgment of the formulary pharmacist and the contents of the locally agreed prescribing guide. The representative was not aware of any new hospital or pharmacy policy forbidding conversation with pharmacy technicians on commercial issues. The representative had always discussed commercial issues in the past with pharmacy staff in the waiting room entrance and this was established practice. The representative did not feel that the complainant was "intervening" in the conversation but simply passing by and making comments on the points of the conversation. The representative did not recall being told to refrain from her discussions in any way and denied that she was complaining about the use or otherwise of the company's products as they were virtually all on the hospital formulary.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant was sent the response from the company and commented further on the matter.

The complainant pointed out that not all the company's products were in the prescribing guide, in particular the product discussed in the way the complainant had found unacceptable. Also named were gastroenterologists, the formulary pharmacist and the prescribing guide contents. The complainant pointed out that a pharmacist other than herself was of course present thus obviating the necessity of the representative talking to a pharmacy technician. In no circumstances should a drug company representative begin to introduce the range of products to a technician. The hospital communication channels with drug companies' representatives were clear. All prescribing guide information and discussions with pharmacy should take place at the district general hospital on behalf of all the hospitals in the trust. The complainant emphasised that her professional concern was with the content of the discussion. If the representative was unclear as to the communication channels this could always be rectified.

The complainant had discussed the matter with the company's regional business manager. The representative had offered to meet with the complainant and apologise but this seemed to the complainant to miss the point. At a time when the NHS was frequently criticised an unguarded conversation such as this was entirely inappropriate and could have easily caused offence and anxiety to both staff, visitors and patients. The complainant hoped that the episode could be used productively to influence the future behaviour of this representative and other representatives. The complainant had no particular problem with the representative continuing to visit the pharmacy providing a professional attitude was consistently maintained.

RULING

The Panel noted that the Code did not in prinicple prohibit representatives from speaking to pharmacy technicians. It would depend upon what was said and whether what was said was in accordance with the Code. Clause 15.4 did, however, require that the arrangements in force at any particular establishment must be observed. In

the Panel's view it was not unacceptable to discuss medicines that were not on a formulary. Companies and their representatives should not, however, unfairly criticise developments in hospitals. The Panel noted that the representative had in the past discussed matters in the waiting room entrance.

The Panel observed that as with all cases of this nature it was difficult to be certain as to what had been said and whether what had been said by the representative was acceptable in relation to the Code. The Panel noted that the representative had denied making critical reference to the judgment of the formulary pharmacist and the contents of the prescribing guide. Clearly the complainant had been upset by the representative's conduct. It would be advisable for the representative to bear the complainant's comments and views in mind in future dealings with the hospitals. The Panel considered, however, that there was not sufficient evidence upon which a ruling of a breach of the Code could be based. Given the circumstances the Panel ruled no breach of the Code.

Complaint received 25 September 1995

Case completed 23 November 1995

CASE AUTH/339/9/95

GENERAL PRACTITIONER v LEO

Fucithalmic mailing

A general practitioner complained that a mailing sent by Leo promoting Fucithalmic was unfair scare marketing. The mailing consisted of a brochure referring to the risks of local application of chloramphenicol and a reprint from the British Medical Journal of an article entitled "Use of chloramphenicol as topical eye medication: time to cry halt? Bone marrow aplasia also occurs with ocular use".

The Panel considered that the presentation in the brochure of facts regarding potential risks with chloramphenicol was misleading and unbalanced. The risks had been overemphasised, given the Committee on Safety of Medicine's data and the recommendation in the British National Formulary that chloramphenicol was the drug of choice for superficial eye infections. The Panel ruled that the mailing as a whole was misleading and disparaged ophthalmic chloramphenicol.

A general practitioner submitted a complaint about a mailing promoting Fucithalmic (fusidic acid) sent by Leo Laboratories Limited to general practitioners.

The mailing consisted of a brochure (ref 2020(i)) which, when unfolded, could be used as a height chart, a reply paid card and a reprint from the British Medical Journal of an article by Doona & Walsh entitled "Use of chloramphenicol as topical eye medication: time to cry halt? Bone marrow aplasia also occurs with ocular use".

One page of the brochure was headed "Fucithalmic Avoids the potential risks of chloramphenicol" followed by a heading "warning" which was followed by two quotations.

Firstly, from the Physicians Desk Reference (USA):

"Bone marrow hypoplasia including aplastic anaemia and death has been reported following local application of **chloramphenicol. Chloramphenicol** should not be used when less potentially dangerous agents would be expected to provide effective treatment."

Secondly, from the Doona & Walsh article published in the British Medical Journal:

"Although the numbers of documented cases of aplastic anaemia associated with topical **chloramphenicol** are few, the tragic consequences in previously healthy patients cannot be ignored. From our review of published reports we find it difficult to justify subjecting patients to this potential risk except when ocular infection is resistant to all other available antibiotics."

COMPLAINT

The complainant was concerned that Leo was sending a copy of a British Medical Journal leading article which suggested that chloramphenicol eye drops were dangerous and should no longer be used. The complainant remembered the article when it appeared and had dismissed it at the time. The complainant contacted the Committee on Safety of Medicines (CSM) to ask if he had missed any new developments regarding the safety of chloramphenicol eye drops. The complainant provided a copy of the reply from the CSM.

The complainant alleged that scare marketing was unfair. There was unlikely to be any mailing from companies producing chloramphenicol eye drops putting the counter argument. Such marketing was putting unfair and unreasonable pressure on GPs and would reduce the resources available which could be used for prescribing new medicines coming on the market. The complainant's own view was that doctors were probably simply prescribing too many eye drops for assumed bacterial infections when most conjunctivitis was entirely viral or quite benign and could be safely treated with more simple measures. Such an approach would be more effective than simply switching from chloramphenicol eye drops to Fucithalmic. Fucidin was known for its hepatic side effects and any such substitution would be swapping the devil known for the unknown. The complainant also considered that Fucithalmic had a narrower spectrum compared to chloramphenicol.

RESPONSE

Leo submitted that the information, claims and comparisons in the brochure were accurate, balanced and fair. There was no attempt to mislead either directly or by

implication. The statements relating to the safety of topical chloramphenicol in the brochure were entirely consistent with the UK data sheet, the Physicians Desk Reference (published in the USA) and the British Medical Journal article. The company submitted that neither the quotation from the Physicians Desk Reference nor the quotation from the British Medical Journal were disparaging of any particular product and both reached the same conclusion that there was a clinical risk of haematological complications following ocular treatment with chloramphenicol.

Leo drew attention to extracts from UK data sheets for ophthalmic chloramphenicol. The data sheet for Chloromycetin (Parke-Davis' product) stated "Bone marrow hypoplasia including aplastic anaemia has been reported following topical use of chloramphenicol. Whilst the hazard is a rare one, it should be borne in mind when assessing the benefits expected from the use of this compound". Leo also referred to the data sheet for Sno Phenicol (Chauvin's product) "Several cases of major adverse haematological events (bone marrow depression, aplastic anaemia and death) have been reported following ocular use of chloramphenicol". Leo submitted that in the light of these statements it was apparent that the brochure could only be considered fair and balanced. The brochure did state that bone marrow hypoplasia and aplastic anaemia were potential risks and that documented cases were few and this was confirmed by the letter from the Committee of Safety of Medicines.

With regard to the article from the British Medical Journal, the company submitted that it did not contain any statement contrary to the product licence for Fucithalmic.

RULING

The Panel noted that the letter from the Committee on Safety of Medicines addressed to the complainant stated that the conclusions of the British Medical Journal article had not been supported by the experts consulted by the CSM. Further since 1966 only eight reports of bone marrow suppression suspected to be associated with ophthalmic chloramphenicol had been reported to the CSM. There had been no deaths attributable to this adverse reaction. Of the eight patients, one was reported as having aplastic anaemia, five had been on long term chloramphenicol to prevent recurrent eye infection with one of these patients taking concurrent medication. Only three reports were received following the use of ophthalmic chloramphenicol for acute conjunctivitis. The letter also stated that the CSM could not give a number for the frequency of bone marrow suppression after ophthalmic chloramphenicol although it believed that this was extremely low because there would have been many millions of prescriptions throughout the UK for ophthalmic chloramphenicol over the last thirty years. The British National Formulary (BNF) stated that chloramphenicol was the drug of choice for superficial eye infections and there was no reason at present to doubt this statement.

The Panel examined the mailing and considered that readers were encouraged to consider the potential risks of using chloramphenicol by both the brochure and the British Medical Journal reprint.

The Panel considered that the presentation in the brochure of the facts regarding potential risks with chloramphenicol was misleading and unbalanced. It considered that the risks of chloramphenicol had been over emphasised given the CSM data and the BNF recommendation that chloramphenicol was the drug of choice for superficial eye infections. Only one side of the argument had been given. The Panel considered that the brochure disparaged ophthalmic chloramphenicol. The Panel considered that its view applied similarly to the distribution of the British Medical Journal article. The Panel therefore ruled that the mailing as a whole was misleading and disparaging in breach of Clauses 7.2 and 8.1 of the Code.

Complaint received **29 September 1995**

Case completed **27 October 1995**

CASE AUTH/340/10/95

DIRECTOR/PARAGRAPH 16 v BOEHRINGER INGELHEIM

Motens promotional aid

The provision of two neck cushions noted by the Panel in its consideration of an earlier case were taken up with Boehringer Ingelheim under Paragraph 16 of the Constitution and Procedure.

The Panel considered that the neck cushions were acceptable on the grounds of cost as each cost the company £1.07. The Panel did not consider, however, that the neck cushions were relevant to the practice of medicine and therefore ruled a breach of the Code.

COMPLAINT

This case arose from a previous matter (Case AUTH/330/9/95) in which the Panel had identified an apparent breach of Clause 18.2 of the Code relating to the provision of the two neck cushions used as a promotional aid for Motens. The matter was taken up under Paragraph 16 of the Constitution and Procedure with Boehringer Ingelheim Limited. The Panel had queried both whether the neck cushions were relevant to the practice of medicine and their cost.

RESPONSE

Boehringer Ingelheim Limited explained that the neck cushions had been offered in a mailing which had consisted of a bulletin "Therapy Express" on hypertension treatment and a reply paid card which offered two inflatable neck cushions for "added comfort during

travel". Doctors had to complete and return a reply paid card.

The company submitted that the unit cost of the neck cushions was £1.07, an inexpensive item and four could theoretically have been sent out on a purely cost basis. In the event it was considered that two would not be excessive. Those creating the mailing in the first place considered that use by physicians with discomfort from neck symptoms was relevant to the practice of medicine and also that the item could be provided to older patients whose hypertension they were treating and who had disability of the neck, a common condition. The company was conscious that it should not suggest a clinical claim for the cushions and therefore settled on the reference to travel. Whether it be patients or their physicians, the cushions were believed to add to the comfort or reduce discomfort during travel.

RULING

The Panel examined the inflatable neck cushion and noted that the product name, Motens, appeared both on the cushion and its case. The Panel noted that Clause 18 of the Code stated that gifts in the form of promotional aids whether related to a particular product or of a general utility could be distributed to members of the health professions provided that such gifts were inexpensive and relevant to the practice of their profession. Inexpensive was defined as costing a company no more than £5 excluding VAT. The Panel noted that the neck cushions were acceptable on the grounds of cost as each cushion cost the company £1.07. The Panel did not consider, however, that the neck cushions were relevant to the practice of medicine and therefore ruled a breach of Clause 18.2 of the Code.

Proceedings commenced **13 September 1995**

Case completed **25 October 1995**

CASE AUTH/365/10/95

PHARMACIST WITH AN NHS BODY v PHARMACIA LEIRAS

Article about Mirena in the lay media

A pharmacist with an NHS body complained about an article in The Guardian regarding Pharmacia-Leiras' new product Mirena. The complainant appreciated that it was sometimes difficult to draw the line between proper and reasonable reporting of new medical interventions in the lay press and that which constituted inappropriate advertising to the public. The complainant alleged that the article might fall into the latter category. The complainant queried a reference in the article to the possibility of extending Mirena's product licence.

In the Panel's view the tone and nature of the information supplied by Pharmacia-Leiras and its public relations agency to The Guardian meant that the information was not factual, nor was it presented in a balanced way and it would encourage patients to ask their doctors to prescribe Mirena. The Panel therefore ruled a breach of the Code. The Panel accepted that the information about the possible extension to the licence had not been provided by the company and therefore ruled no breach of the Code in this regard.

COMPLAINT

A pharmacist with an NHS body complained about an article entitled "Pssst. Wanna buy a new contraceptive?" which appeared in The Guardian, 19 September 1995.

The article discussed Pharmacia-Leiras Limited's new product, Mirena, and the complainant said it was difficult to know whether the article was a piece of genuine reporting by the authors or something which had been written in response to inappropriate promotion by Pharmacia-Leiras.

The complainant pointed out that the first few paragraphs of the article concentrated on the problems some women had had requesting their doctors to prescribe Mirena. The middle part of the article contained details about the device that could be considered to be promotional. The eighth paragraph listed a number of facts/advantages of Mirena which would require the authors to have had access to detailed information about the product. The article also stated that although Mirena could only be used for three years it looked likely that the licence would be extended to five years. Finally, a telephone number was given so that women could contact the manufacturer for more information. The complainant had no objection to existing users being able to obtain information from the manufacturer providing this did not interfere with the patient/doctor relationship. It might not be appropriate for women who had not used the device to be encouraged to contact the company in this way.

The complainant appreciated that it was sometimes difficult to draw the line between proper and reasonable reporting of new medical interventions in the lay press, including medicines, and that which constituted inappropriate advertising to the public. The complainant alleged that the article might fall into the latter category.

RESPONSE

Pharmacia, although not a member of the ABPI, had nevertheless agreed to comply with the Code. The product licence for Mirena was held by Leiras Oy of Finland and it was marketed by Pharmacia-Leiras Limited.

Pharmacia-Leiras submitted that the article in The Guardian was written by two journalists employed by The Guardian. Pharmacia-Leiras could not be responsible for the content of the article. It accepted, however, that it was responsible for the information on Mirena supplied to

the journalists. The company had been in communication with one of the authors who was a freelance journalist. The company believed the journalist contacted its agency by telephone requesting information on Mirena and contact names she could interview. The journalist was supplied with the media information which was distributed at the Mirena press conference on 17 May 1995. The name of a doctor who was suitable expert was given to the journalist. The Family Planning Association was suggested as another contact point.

Pharmacia-Leiras pointed out that there was incorrect information in the article. Firstly, the price, and, secondly, the suggestion that the public could receive information from Pharmacia-Leiras. These two issues were dealt with by the agency which wrote letters to the journalist, the Family Planning Association and The Guardian. Copies of these letters were provided. The telephone number of Pharmacia-Leiras had been given to the journalist by the Family Planning Association. The journalist was unaware that it was intended only for the medical profession.

The company submitted that the information regarding the planned application for an extended licence from 3 to 5 years had been obtained by the journalist from the Margaret Pyke Centre.

RULING

The Panel noted that complaints concerning articles appearing in the lay media were judged on the information provided by the company to the journalist and not on the content of the article itself.

The Panel examined the information provided by Pharmacia-Leiras' agency to the journalist which consisted of two folders both headed "Mirena Contraception for the 21st Century".

The first folder included three media information papers. One headed "Contraceptive for the 21st Century Launched Today" which referred to Mirena as "... the most significant advance in reversible contraception since the invention of the pill". The second media information paper was headed "Mirena: The Facts" which gave a list of features and concluded with the claim "Mirena = contraception for the 21st century". The third media information paper was headed "Contraception: The way forward" and listed a number of hypothetical factors which, in unison, would constitute the ideal contraceptive for women. These were; "100% safe, with neither dangerous nor annoying side effects, 100% effective, independent of intercourse, fully reversible, simple and painless procedure of use or fitting, inexpensive, independent of medical profession and acceptable to every culture, religion and political view." The document went on to state that "Mirena poses an opportunity for women today to have the closest thing available to The Ideal Contraceptive". Abbreviated prescribing information, biographies of certain individuals and a sheet detailing the availability of seven transparencies to support articles were also included in the folder.

The second folder gave more details about contraception generally including a section on current choices which refered to a number of methods and a section on trends in contraception. There was a section on Mirena with information on its mode of action, efficacy, tolerability and suitable candidates. Another section included a patient testimonial and other case histories. Details were given about the Family Planning Association and the Margaret Pyke Centre.

The Panel noted from the response that one of the journalists had apparently contacted Pharmacia-Leiras' public relations agency, and as a result had been given information. There were no details about the actual telephone conversation. Under the Code Pharmacia-Leiras was responsible for the activities of its agency.

The Panel considered that the launch of a new form of contraceptive would be of great interest to the general public. Material issued regarding Mirena needed to comply with Clauses 20 of the Code. Clause 20.1 of the Code stated that prescription only medicines must not be advertised to the general public. Clause 20.2 of the Code required any information about medicines made available to the general public to be factual and presented in a balanced way so as to avoid the risks of raising unfounded hopes of successful treatment or of misleading with respect to the safety of the product. Statements could not be made for the purpose of encouraging members of the public to ask their doctors to prescribe a specific medicine.

The Panel considered that the material supplied by Pharmacia-Leiras went beyond that permitted under Clause 20 of the Code. In this regard the Panel noted claims such as "The most significant advance in reversible contraception", "Mirena = Contraception for the 21st Century" and to Mirena being "... the closest thing available to "The Ideal Contraceptive"".

In the Panel's view the tone and nature of the information meant that it was not factual, nor was it presented in a balanced way and it would encourage patients to ask their doctors to prescribe Mirena. The Panel therefore ruled a breach of Clause 20.2 of the Code.

The Panel noted that the information about the possible extension to Mirena's licence had not been provided by the company. The journalist had obtained the information from the Margaret Pyke Centre. The Panel therefore ruled no breach of Clause 3.2 of the Code.

The Panel noted that the article included the telephone number of the company. The journalist had been given the number by the Family Planning Association. The Panel was very concerned that the company would be receiving calls from members of the public who had read the article. No information had been supplied by the company as to the action taken when such calls were received. In the Panel's view the company needed to take great care to ensure that Mirena was not advertised to callers which, given the circumstances, would be very difficult to achieve. Information given to callers either verbally or in writing would need to comply with Clause 20 of the Code.

Complaint received **25 October 1995**

Case completed **29 November 1995**

CASES

315/6/95	SmithKline Beecham v Pfizer	Lustral detail aids	Breach 7.2	Appeal by respondent
316/7/95	Ethics committee chairman v Servier	Study using Coversyl & Natrilix	Breach 10.2 & 18.1	Appeal by respondent
318/7/95 321/7/95 322/7/95	Hospital personnel Anon hospital doctor Hospital doctor v Knoll	Conduct of a representative	Outside Code Breach 2 & 15.2 Outside Code	) Appeal by respondent))
324/8/95	Ciba v Solvay	Fematrix detail aid	Breach 7.2, 7.6 & 7.7	Appeal by respondent
332/9/95	Pfizer v Knoll	Securon SR cost comparison chart	Breach 7.2	No Appeal
333/9/95	GP v Member company	Patient information leaflet	No breach	No appeal
334/9/95	GP v Roche	Information on malaria	Breach 20.2	No appeal
335/9/95	Hospital doctor v Knoll	Gopten journal advertisement	Breach 3.2 & 7.2	No appeal
337/9/95	Hospital pharmacist v Member company	Conduct of a representative	No breach	No appeal
339/9/95	GP v Leo	Fucithalmic mailing	Breach 7.2, 8.1	No appeal
340/10/95	Director/Paragraph 16 v Boehringer Ingelheim	Motens promotional aid	Breach 18.2	No appeal
365/10/95	Pharmacist with a NHS body v Pharmacia Leiras	Article about Mirena in lay media	Breach 20.2	No appeal

PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

The Prescription Medicines Code of Practice Authority was established by The Association of the British Pharmaceutical Industry (ABPI) in 1993 to operate the Code of Practice for the Pharmaceutical Industry at arm's length from the ABPI itself.

Compliance with the Code is obligatory for ABPI member companies and, in addition, more than fifty non member companies have voluntarily agreed to comply with the Code and to accept the jurisdiction of the Authority.

The Code covers the advertising of medicines to health professionals and administrative staff and also covers information about such medicines made available to the general public.

It covers:

- journal and direct mail advertising
- the activities of representatives including detail aids and other printed material used by representatives
- the supply of samples
- the provision of inducements to prescribe, supply or buy medicines by the gift, offer or promise of any benefit or bonus, whether in money or in kind
- the provision of hospitality for promotional purposes
- the sponsorship of promotional meetings
- the sponsorship of scientific meetings including payment of travelling and accommodation expenses in connection therewith
- the provision of information to the general public either directly or indirectly
- all other sales promotion in whatever form, such as participation in exhibitions, the use of audio-cassettes, films, records, tapes, video recordings, electronic media, interactive data systems and the like.

Complaints submitted under the Code are considered by the Code of Practice Panel which consists of the three members of the Code of Practice Authority acting with the assistance of independent expert advisers where appropriate. Both complainants and respondents may appeal to the Code of Practice Appeal Board against rulings made by the Panel. The Code of Practice Appeal Board is chaired by an independent legally qualified Chairman, Mr Philip Cox QC, and includes independent members from outside the industry.

In each case where a breach of the Code is ruled, the company concerned must give an undertaking that the practice in question has ceased forthwith and that all possible steps have been taken to avoid a similar breach in the future. An undertaking must be accompanied by details of the action taken to implement the ruling. Additional sanctions are imposed in serious cases.

Complaints about the promotion of medicines should be sent to the Director of the Prescription Medicines Code of Practice Authority, 12 Whitehall, London SW1A 2DY (telephone 0171-930 9677 facsimile 0171-930 4554).