PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

NUMBER 16

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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.

Out with the old...

David Massam, the Director of the Authority since its inception in 1993, retired at the end of April though he will remain as a consultant to the Authority for a little while. David joined The Association of the British Pharmaceutical Industry (ABPI) in 1970 and was its Secretary from the beginning of 1982 to the end of 1992 when he became Director of the Authority. He was involved with the Code of Practice for the whole of that time. He was also Executive Director of Datapharm Publications Limited which is responsible for publishing the ABPI Data Sheet Compendium from 1977 to 1992 and remained a Director until 1997.

David has made an enormous contribution to the pharmaceutical industry during the last 27 years, which has been a time of significant change for the industry and its customers. David is probably the world expert on matters relating to self regulation of advertising. He has been involved with both the IFPMA Code of Pharmaceutical Marketing Practices and the EFPIA European Code of Practice for the Promotion of Medicines. His wise counsel will be missed by all his colleagues who will no doubt join the Authority in thanking him for his work and wishing him a long and happy retirement.

.....in with the new

David Massam has been succeeded as Director of the Authority by Mrs Heather Simmonds, who was formerly its Secretary. Heather joined the ABPI in 1984 and has worked on the Code of Practice since 1989. She moved from the ABPI to the Authority when it was established in 1993. She holds an Honours Degree in Pharmacology from the University of Leeds.

Representatives bearing gifts

A medical representative who calls upon a doctor to deliver an item, such as a requested monograph or promotional aid, must not make getting to see the doctor a precondition of leaving the item.

Having indicated that he or she has called upon the doctor with a view to leaving the item, the representative must leave it even though he or she does not get to see the doctor. Taking the item away in such circumstances amounts to a breach of Clause 15.3 of the Code.

Membership of the Code of Practice Appeal Board

There are twelve industry members on the Code of Practice Appeal Board, all of whom must be senior executives in the industry and four of whom must be medically qualified. Membership of the Appeal Board involves a substantial commitment as the Appeal Board meets about ten times a year for a full day on each occasion and the reading of substantial paperwork is required in advance. Nonetheless, members of the Appeal Board find it to be an interesting and stimulating activity.

Vacancies arise from time to time and the Authority would be interested to hear from industry executives who feel that they are sufficiently widely experienced to be appointed and who are willing and able to devote adequate time to the activity.

The Authority's levy

The Authority has been required to be self-financing since the beginning of 1996, at which time its charges were increased and the subscriptions of the ABPI, which had previously subsidised the Authority, were correspondingly decreased.

At the ABPI's Annual General Meeting on 9 April, members passed a fresh resolution relating to the Authority's levy. This was necessary because of recent changes to the ABPI Rules of the Constitution which meant that it no longer had Associate Members.

The levy is now £1,000 per annum for those ABPI Members whose turnover has not reached the basic threshold (£2.5m), £4,000 per annum for One Vote Members and £8,000 for Two Vote Members. In 1997 only, there will be transitional charges of £2,000 and £6,000 respectively if a company has moved up from one category to another.

The Authority had a net surplus of £65,588 in 1996. The Authority's income is very difficult to predict as it is partially dependent on the level and number of administrative charges. If the Authority has increasing surpluses, its income will be adjusted downwards in appropriate years by calling up only a proportion of the levy.

"Advertorials"

There has been a notable increase in recent months in the number of advertisements which have the general appearance of editorial material, sometimes referred to as "advertorials".

These usually have the word "advertisement" or "advertisement feature" or similar at the top but companies are advised that this will not necessarily be sufficient to prevent the material from being regarded as disguised promotion. Even if such words appear at the top, such an advertisement may be regarded as disguised promotion if the general appearance and layout is similar to that of the actual editorial material in the journal concerned. There must be adequate differentiation.

Non-promotional meetings

Companies are reminded that Clause 19 of the Code relating to meetings applies equally to both promotional meetings and non-promotional meetings. Thus, it covers meetings of clinical trialists and the like. This does not mean that such non-promotional meetings are covered by the generality of the Code as a meeting of clinical trialists would, for example, almost inevitably discuss unlicensed indications. What it does mean, however, is that the requirements as to the hospitality being of a reasonable standard etc which are set out in Clause 19 apply as they do to other meetings.

Declaration of sponsorship

Clause 9.9 of the Code states that "All material relating to medicines and their uses which is sponsored by a pharmaceutical company must clearly indicate that it has been sponsored by that company".

This requirement is not satisfied in respect of a publication by hiding the fact of sponsorship in small print at the bottom of a page so that it is unlikely to be seen by those reading the material in question. Sponsorship must be indicated in a reasonably prominent up-front manner so that it will be seen by readers before they read the publication.

Summaries of product characteristics

Companies are advised that it is not permissible for summaries of product characteristics to bear promotional slogans and the like for the product concerned. The Medicines Control Agency regards this as incompatible with the legal requirements for SPCs.

CODE OF PRACTICE TRAINING

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

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

Forthcoming Code of Practice seminar dates are:

Thursday, 10 July 1997
Tuesday, 9 September 1997
Tuesday, 21 October 1997

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 Flynn for details (0171-930 9677 extn 1443).

How to contact the Authority

Our address is:

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

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

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

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

Heather Simmonds 0171-839 1058 (until 11 June) 0171-747 1438 (from 12 June)

Jane Landles 0171-747 1415

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

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

CASE AUTH/472/10/96

SEARLE v ASTA MEDICA

Promotion of Zamadol

Searle complained about the promotion of Zamadol (tramadol) by Asta Medica.

The Panel ruled that it was misleading to claim that 50mg of tramadol was approximately equal to 100mg of codeine. On appeal by Asta Medica, the Appeal Board considered that the 100mg dose of codeine used was too high and too specific given the currently available data. The claim was ruled to be misleading. The Panel ruled that a claim "The right analgesic profile" was all embracing in breach of the Code. This ruling was upheld on appeal by Asta Medica.

A statement referring to the dosage regimen was ruled not to be unreasonable. Breaches were ruled in relation to the use of the words "unique" and "safe". A reference to long term use of Zamadol was ruled to be misleading as the warnings in the SPC were not given.

Searle complained about the promotion of Zamadol (tramadol) by Asta Medica Limited. Asta Medica was not a member of the ABPI but had nevertheless agreed to comply with the Code.

The items at issue were a Zamadol detail aid (ref 600/8/1996), a Zamadol "Questions & Answers" booklet (ref 622/8/96) and a Zamadol leavepiece headed "Managing the Cost" (ref 606/8/96). There were a number of allegations which were considered as follows:

1 Dose of Zamadol equivalent to dose of codeine

COMPLAINT

Searle drew attention to two statements. Firstly, in the detail aid a claim that 50mg Zamadol was approximately equal to 100mg codeine, and, secondly, a statement in the "Questions & Answers" booklet that "... 50mg of tramadol is therefore approximately equivalent to 100mg of codeine."

Searle alleged that the claim that 50mg Zamadol was approximately equal to 100mg codeine was factually incorrect and misleading with regard to the relative potencies of the two products. The only accurate and clinically accepted method to assess which dose of one analgesic equated to the dose of another analgesic was to assess them in the controlled double blind clinical trial situation. This had been done and a large body of clinical data existed, including 17 studies involving 3453 patients treated for post surgical and post dental extraction pain. In these studies, single doses of tramadol (50mg, 75mg, 100mg, 150mg and 200mg) were compared with single doses of other analgesic agents including codeine 60mg. A meta analysis of this large pool of clinical data had shown unequivocally that a dose of 50mg tramadol equated most closely with 60mg codeine (Sunshine).

Searle referred to three subsequent statements in the detail aid that "Each 50mg Zamadol capsule ... provides analgesia equivalent to more than 3 codeine 30mg tablets", "Just one 50mg Zamadol capsule q.d.s. ... provides analgesia greater than the maximum daily dose of codeine" and a visual representation of 8 tramadol 50mg capsules followed by the approximately equal symbol then "More than three times the permitted daily analgesic dose of codeine alone". A reference was given to Twycross which included a table headed "Approximate oral analgesic equivalence to morphine". This table only showed potency ratios of morphine with tramadol and with codeine individually. It did not show a direct comparison of tramadol with codeine but did extrapolate within the text to give such a figure. This extrapolation from an approximation could only accentuate the potential inaccuracy inherent in the original approximation. A breach of Clause 7.2 of the Code was alleged.

RESPONSE

Asta Medica pointed out that the detail aid referred to 50mg of Zamadol being approximately equivalent to 100mg of codeine. The claim was based on Twycross who stated that tramadol was regarded as double strength codeine. Asta Medica agreed that the double blind controlled clinical trial was recognised as the method of determining direct equivalent activity between two products. There were, however, in the pain model in human subjects enormous individual variances. These were well documented when reviewing the data in the review by Sunshine referred to by Searle. This review summarised the single dose data for various doses of tramadol, against codeine and placebo. Asta Medica pointed out that the mean sum of the pain intensity difference (SPID) scores showed that placebo produced the same results as tramadol 50mg and codeine 60mg. This was clearly not the case in clinical practice or in other studies using the two products. Looking at the data in the dental pain model, which was widely recognised as a reference for medicine/pain assessment, all 54 studies quoted by Sunshine in his meta analysis showed that tramadol 50mg was superior to codeine 60mg. When taken in conjunction with the Twycross statement that tramadol was regarded as double strength codeine, the company submitted that it was justified in using an approximate equivalence.

Asta Medica criticised meta analysis as such procedures were recognised to be of lesser or even doubtful value statistically owing to inherent flaws in comparing data sets from studies of different design and parameter, although in the same field.

Asta Medica pointed out that the studies referred to by Sunshine were single dose studies whereas clinical practice usually involved multiple dosing. Tramadol as a single oral dose had a bioavailability of approximately 68% while in multiple administration this rose to approximately 90 - 100%. This would therefore justify the claim that tramadol was approximately double strength codeine.

Pain was a largely subjective sensation, difficult to quantify in units, modified not only pharmacologically but on a multifactorial basis physiologically and psychologically. Hence trying to equate clinical study results from a meta analysis dealing with single dose studies to multiple dosing where the external pharmacological factors assumed a greater role could only be described as an approximation at best unless the external factors could be quantified.

PANEL RULING

The Panel agreed that the most appropriate method of determining direct equivalent activity of different products was by way of controlled double blind clinical trials. There appeared to be no study comparing tramadol and codeine on an acute or chronic basis. The Sunshine studies were single dose.

The Panel noted that the Twycross data stated that tramadol's ".... exact relative potency with oral codeine and oral morphine in cancer patients is still debatable". In the Panel's view, it was not acceptable to calculate the approximate equivalent doses of tramadol and codeine by way of a calculation in relation to each medicine's potency compared to morphine as had been done by Asta Medica. No details of the doses of tramadol and codeine used when calculating their relative potencies with morphine were given in the Twycross data.

The Panel considered that it was misleading to claim that 50mg of tramadol was approximately equal to 100mg of codeine as stated in the detail aid. A breach of Clause 7.2 of the Code was ruled. This ruling also applied to the "Questions & Answers" booklet which, although not as dogmatic as the detail aid, was also considered to be misleading.

The Panel noted that its ruling would apply also to the bullet points listed in the detail aid.

APPEAL BY ASTA MEDICA

Asta Medica submitted that Budd, a recognised expert, said that tramadol was superior to codeine and would render the performing of a study comparing tramadol and codeine doubtful in terms of ethics and the amount of data already available on the analgesic efficacy of tramadol, morphine and codeine.

Asta Medica referred to the previous rulings in Case AUTH/184/7/94 when Sanofi Winthrop levelled similar charges against Searle. The Appeal Board had accepted that Searle had sufficient evidence to show that Zydol (tramadol) was "more effective than codeine". Searle had submitted that its data had shown that tramadol 75mg and 100mg were statistically significantly better than codeine 60mg and that 50mg tramadol was numerically better in three of four studies. Searle also submitted that comparing tramadol 50mg and codeine 60mg was not a comparison of like with like as tramadol's minimal effective dose was being compared with the highest recommended dose of codeine. The company also drew the attention of the Appeal Board to the inherent problems associated with pain studies. The Appeal Board had accepted that tramadol was more effective than codeine. Having accepted this principle, Asta Medica wanted to convince the Appeal Board that it was justifiable to state in the case now before it that 50mg oral tramadol was approximately equal to 100mg codeine. The Panel had ruled that the Twycross data used in the detail aid was not acceptable as Twycross stated that for tramadol "... the exact relative potency with oral codeine and oral morphine in cancer patients is still debatable". The Panel's view was that it was not acceptable to calculate the approximate equivalent doses of tramadol and codeine by way of a calculation in relation to each medicine's potency compared with morphine.

Asta Medica said that it was standard practice to compare one analgesic to another by relating its analgesic effect to that of morphine. The British National Formulary stated that "... morphine is the standard against which opioid analgesics are compared", Twycross stated in his book and in a recent personal communication, that potency ratios were approximate, as did all other authors presenting equipotency tables and this was reflected in the detail aid.

Asta Medica submitted that owing to the multifactorial nature of pain, accurate clinical measurement of pain intensity and reduction of pain was not possible. The psychological factors that play such a great part in the response to both pain and treatment vary intra-individually. Analgesia must be continuously assessed and tailored to each individual. From this, it was clear that any exact comparison of potency, however scientifically desirable, was ultimately not clinically possible. Hence all authors listing equivalent potencies used approximations and Twycross clearly stated that the equivalent potencies, based on equivalence to morphine, were approximate. He was justified in using these approximations in his lectures on the grounds of his extensive clinical experience confirming the data derived from the studies in the literature. Asta Medica noted that the Panel was concerned about the lack of reference in the Twycross publication to the doses of tramadol and codeine used when calculating their relative potencies with morphine. The clinical studies used to support the claim confirmed that the potency ratio of oral tramadol to oral codeine was approximately 1:2 ie 50mg tramadol was approximately equal to 100mg codeine in terms of analgesic response. The company provided a number of papers to support the claim.

In conclusion Asta Medica said that it had demonstrated that the use of morphine as a reference compound to compare the equipotency of codeine and tramadol was justified and conformed to accepted medical practice for analagesia and that the use of the data from Twycross that 50mg tramadol was approximately equal to 100mg of codeine was correct and was a summary of the available knowledge as demonstrated in the studies provided.

The company never intended to make a definite statement about the dose of Zamadol and codeine. The detail aid was designed to answer GP questions about where Zamadol fitted in compared to other analgesics. The company said that in the dental pain studies, the ratio of Zamadol:codeine was approximately 1:1.2. With moderate to severe pain the ratio was approximately 1:2. More data would be available shortly.

APPEAL BOARD RULING

The Appeal Board noted that pain was a subjective matter

and that it was helpful to provide information for doctors as to where Zamadol fitted in with other analgesics. It noted that there was no study comparing 50mg of Zamadol with 100mg of codeine. The difference in the ratio of Zamadol to codeine appeared to depend on whether the products were used on an acute or chronic basis. This had not been mentioned in the detail aid. The relevant page would be read as applying to the relief of pain on both an acute and a chronic basis. It would have been more helpful if the data had been more fully explained in the detail aid and perhaps a range given rather than the use of the approximately equal symbol.

The Appeal Board did not agree with the Panel's view that it was not acceptable to calculate the approximate equivalent doses of tramadol and codeine by way of a calculation in relation to each medicine's potency compared to morphine.

The Appeal Board did, however, consider that the detail aid was misleading as the 100mg dose of codeine used was, in its view, too high and too specific given the currently available data. A breach of Clause 7.2 of the Code was ruled.

The Appeal Board considered that its ruling also applied to the "Questions & Answers" booklet.

The appeal on this point therefore failed.

2 Claim "The right analgesic profile"

This claim appeared in both the detail aid and the leavepiece. The relevant double page in the detail aid was headed "Zamadol for the right reasons". The left hand page was headed "The right analgesic profile" and the right hand page was headed "... at the right price". The page headed "The right analgesic profile" was followed by six bullet points. Five were general points and the other was "Very low evidence of addictive potential in 15 years use". The page in the leavepiece was headed "Zamadol for the right medical reasons" followed by the claim "The right analgesic profile" followed by three bullet points and the statement "Clinically proven in chronic & acute moderate - severe pain".

COMPLAINT

Searle alleged that the claim "The right analgesic profile" was all embracing in breach of Clause 7.8 of the Code.

RESPONSE

Asta Medica submitted that when the claim was viewed in context it read "The right analgesic profile .... for the right reasons .... at the right price" and was qualified immediately below on both pages of the detail aid by listing the requirements for an analgesic with references to back up the claims for these. The claim was not for the analgesic as mentioned in the supplementary information to Clause 7.8 implying best but rather as the right choice for the reasons listed below the claim which qualified the word "right". The company was not indicating that Zamadol was the only or best analgesic but that it was one which fitted the criteria required of an analgesic.

PANEL RULING

The Panel considered that the claim "The right analgesic profile" was not referring merely to the features associated with an analgesic. The layout and content of both the detail aid and the leavepiece were such that the features listed were in effect claiming that Zamadol had the right analgesic profile. The Panel considered that the claim was all embracing and ruled a breach of Clause 7.8 of the Code with respect to both the detail aid and the leavepiece.

APPEAL BY ASTA MEDICA

Asta Medica submitted that to read the claim in isolation took it out of context. The page from the detail aid where the claim appeared had to be viewed together with the material below it and the material on the adjacent page. Zamadol was introduced in the detail aid as a powerful new alternative to strong co-analgesics in managing patients in pain, for the right reasons. This was expanded on the double page in question where the reasons were that it had the right analgesic profile ... at the right price (to manage patients in pain).

Of the four words used in the claim "The right analgesic profile" the word which deserved the most attention was "profile" which was defined as "a graph, table, etc., representing the extent to which a person, field, or object exhibits various tested characteristics". Beneath the claim, an analgesic profile was described. Asta Medica had described this profile as the "right" one (definition from Collins Concise Dictionary "appropriate, suitable, correct in opinion or judgement") using a Budd reference where the following statement regarding an analgesic profile was made:

"Evidently, there is a need for an agent that can provide adequate efficacy across the broad spectrum of pain types together with a clinically acceptable adverse reaction profile. It should also offer a low potential for the development of tolerance to its analgesic effect, an absence of addictive potential, and few, if any, interactions with other drugs. For ease of use, a variety of formulations should be available".

Budd then went on to say:

"Tramadol has been shown to possess a number of these qualities ....".

By having the picture of Zamadol capsules immediately below the claim it was implied that Zamadol had this desirable profile. However, no reference or inference was made to Zamadol being the only analgesic to fulfil the criteria, and on the adjacent page, a cost comparison was shown with a paracetamol/codeine combination which must, by its inclusion, also be considered as having the right analgesic profile.

There was no implication that Zamadol had the best profile for an analgesic drug which could be considered to have no drug interactions, no tolerance or dependence, superlative efficacy etc. What was being indicated was that it had the right kind of profile ie a desirable profile for an analgesic. Zamadol did fulfil the majority of the criteria for the right analgesic as referenced on the page. The use of the word "right" was in common use regarding analgesics.

The company submitted that it had used accepted, published medical terminology in a relevant fashion to describe the role that its product had to play, with others, in the field of moderate to severe pain.

APPEAL BOARD RULING

The Appeal Board noted that material could list features of the right analgesic profile and then state how a particular product matched up to that profile. It was important to separate the two elements as otherwise the material would claim that a particular product had the right analgesic profile and this was not permitted under the Code. The Appeal Board considered that the features of the right analgesic profile had not been separated sufficiently from how Zamadol measured up to that profile. The layout and content meant that the detail aid was claiming that Zamadol had the right analgesic profile. This was an all embracing claim. The Appeal Board therefore upheld the Panel's ruling of a breach of Clause 7.8 with respect to both the detail aid and the leavepiece.

The appeal on this point therefore failed.

3 Dosage regimen

Attention was drawn to a claim in the detail aid "Flexible dosage - 50mg p.r.n., 4-6 hourly up to 400mg in divided doses" and a section in the "Questions & Answers" booklet which gave the dosage range as "Starting at a dose of 50mg PRN, every 4-6 hours, up to a maximum of 8 capsules (400mg) daily in divided doses".

COMPLAINT

Searle alleged that the statement in the detail aid was ambiguous, misleading and inconsistent with the dosage recommendation in the Zamadol abbreviated prescribing information and summary of product characteristics (SPC). The adult dose for Zamadol was one or two 50mg capsules every 4-6 hours, up to a total daily dose of 400mg. It was not, as in the detail aid, 50mg, or, when required 4-6 hourly up to 400mg daily. A breach of Clause 7.2 of the Code was alleged.

RESPONSE

Asta Medica pointed out that the SPC stated "The capsules are for oral administration. As with all analgesic drugs the dosing of Zamadol capsules 50mg should be adjusted depending on the severity of the pain and the individual clinical response of the patient". The dosage instructions for adults were "For acute pain an initial dose of 100mg is usually required. For chronic painful conditions an initial dose of 50mg is recommended. Subsequent doses should be 50mg to 100mg administered 4-6 hourly. The dose level and frequency of dosing will depend on the severity of the pain. The capsules should only be administered where there is a medical need for pain relief and treatment should normally be for a limited period and intermittent".

Asta Medica submitted that there were choices built into the dosage schedule which was not fixed. The latin abbreviation prn was defined as occasionally or when required, implying the dosing was dependent on the need for pain relief. Twycross stated that the right dose of an analgesic was the dose which relieved pain and that relief should be evaluated in relation to each pain. Accepted clinical and pharmacological management of pain had long had to take into account the individual variability of response to pain medication. Having taken the variability of need for analgesic into account and the SPC, the addition of the qualifying reference to "prn" had clarified rather than confused.

PANEL RULING

The Panel noted that the SPC did not refer to "prn" as given in the detail aid and the "Questions & Answers" booklet. The Panel decided that the statement "Flexible dosage - 50mg p.r.n., 4-6 hourly up to 400mg in divided doses" in the detail aid and "Starting at a dose of 50mg PRN, every 4-6 hours, up to a maximum of 8 capsules (400mg) daily in divided dose" in the "Questions & Answers" booklet were not unreasonable given the SPC. The Panel therefore ruled no breach of Clause 7.2 of the Code.

4 Statement "... indicate that tramadol is a unique opioid of significant clinical potential"

This statement appeared in the "Questions & Answers" booklet in the answer to a question "Why should I use Zamadol over other opioids?".

COMPLAINT

Searle alleged that the description of tramadol as a unique opioid was an exaggerated claim in breach of Clause 7.8 of the Code.

RESPONSE

Asta Medica submitted that a paper by Budd described tramadol as a unique opioid due to its lower adverse event profile. Its dual mode of action as an opioid and a 5-HT reuptake inhibitor led to fewer opioid side effects when compared with a pure opioid such as morphine, due to a weak affinity to certain receptors, while still producing the required pain relief equated with a stronger opioid. As tramadol was the only registered medication which had both opioid and 5-HT reuptake inhibitory action it was not therefore unreasonable for Budd to describe tramadol as a unique opioid. Asta Medica said that it had not breached Clause 7.8 by using Budd's description of tramadol.

PANEL RULING

The Panel noted that it was not necessarily acceptable to repeat what Budd had said about tramadol in promotional material. It was not acceptable to quote an expert or refer to an expert's opinion in promotional material if it would be in breach of the Code.

The Panel noted that the supplementary information to Clause 7.8 referred to the word "unique". It stated that great care needed to be taken with the use of the word. Although in some circumstances the word "unique" may be used to describe some clearly defined special feature of a medicine, in many instances it may simply imply a general superiority. In such instances it was not possible

to substantiate the claim as the claim itself was so ill defined.

The Panel noted that the relevant section of the "Questions & Answers" booklet stated "The minimal likelihood of tolerance, physical dependence, lack of respiratory and circulatory depression, in addition to a low constipating effect, indicate that tramadol is a unique opioid of significant clinical potential".

The Panel considered that every product was unique in its own way in a general sense but the only way the word could be used in promotional material was when it was referred to a specific feature. The Panel considered that in this instance the word "unique" had been used to imply a general superiority which was prohibited. A breach of Clause 7.8 of the Code was ruled.

5 Statement "Zamadol capsules are a safe and effective alternative ..."

The statement appeared in the "Questions & Answers" booklet.

COMPLAINT

Searle alleged that the statement "Zamadol capsules are a safe and effective alternative to any other current non-narcotic analgesic..." was in breach of Clause 7.7 of the Code.

RESPONSE

Asta Medica said it was aware that the use of the word "safe" was restricted, the sentence referred to the published words of Budd and hence was considered to be justified bearing in mind that a full list of side effects was given in the same section of the booklet. Sunshine presented certain comparative efficacy data and concluded that tramadol "... proved to be an effective analgesic with good tolerability" ie the safety of a low profile of side effects.

PANEL RULING

The Panel noted that it was not acceptable to quote an expert or refer to an expert's opinion in promotional material if it would be in breach of the Code.

The Panel noted that Clause 7.7 prohibited the use of the word "safe" without qualification. The use of the word "safe" had not been qualified and the Panel therefore ruled a breach of Clause 7.7 of the Code.

6 Question "Can I use Zamadol long term?"

This question appeared in the "Questions & Answers" booklet. The answer given was "Yes, clinical studies have established the efficacy and safety of tramadol in chronic use. Studies of up to 52 weeks of continuous exposure reveal no long term problems with its use".

COMPLAINT

Searle alleged that the answer to the question implied that Zamadol could be used for up to 52 weeks. This did not equate with the SPC recommendations for limited and intermittent use. Searle alleged that the product was being promoted outside the terms of the marketing authorisation in breach of Clause 3.2 of the Code.

RESPONSE

Asta Medica said that the SPC clearly stated that treatment should normally be for a limited period and the wording "should" in the SPC and "can" in the "Questions & Answers" booklet should be considered carefully. The use of the word "can" did not imply normal usage, but that it was possible in a case of medical need to use the product continually and for a longer period. As chronic pain was mentioned in the adult posology in the SPC, there was likely to be use of the product either continually or on an intermittent basis for a prolonged period of time in dealing with pain relief where there was a medical need and the medicine was still effective in a small cohort of patients.

To enable the doctor to make an educated assessment of risk versus benefit of any treatment, the doctor needed to know whether dosing duration had been considered or performed previously and what was the risk versus benefit. Studies in cancer pain, such as that by Rodrigues and Pereira described the use of tramadol on a long term basis in a cohort of patients, with three having had treatment for as long as 26 months. Thus the company was justified in telling the physician that tramadol had been used long term with no additional problems above those of short term therapy.

PANEL RULING

The Panel noted that the SPC stated that "The capsules should only be administered where there is a medical need for pain relief and treatment should normally be for a limited period and intermittent". The product was licensed for chronic and acute pain. The Panel considered that the statement in the "Questions & Answers" booklet should have included more detailed information in the light of the statement in the SPC. The Panel considered that the "Questions & Answers" booklet was misleading in that it did not repeat the warnings in the SPC and therefore ruled a breach of Clause 7.2 of the Code.

Complaint received **17 October 1996**

Case completed **14 February 1997**

CHAIR, RESEARCH ETHICS COMMITTEE v SOLVAY

Physiotens study

The chair of a research ethics committee complained about a clinical study on Physiotens (moxonidine) carried out by Solvay Healthcare Limited. The research ethics committee was concerned that the study was promotional.

The Panel had some concerns about the recruitment of the study population but considered that the study was not promotional in nature. No breach of the Code was ruled.

The chair of a reasearch ethics committee complained about a clinical study on Physiotens (moxonidine) conducted by Solvay Healthcare Limited (Physiotens Study S2203103). The purpose of the study described by the protocol was to evaluate and compare combination treatment of 400 micrograms of Physiotens with hydrochlorothiazide, enalapril or amlodipine in hypertensive patients unresponsive to monotherapy with 400 mcg of Physiotens.

The protocol described the study as consisting of two phases. An open phase of 4 weeks' placebo run in followed by 8 weeks' active treatment with Physiotens. Randomization to the 4 weeks' double blind phase, with the different add on therapies, would take place for non responders to monotherapy. One thousand patients were needed for the UK part of the study.

COMPLAINT

The research ethics committee was concerned that this was a promotional exercise aimed at recruiting approximately 200 general practitioners to prescribe moxonidine to 1000 patients, coinciding with the launch of the product.

The trial's inclusion criteria allowed patients on an established anti-hypertensive agent to have that treatment discontinued and to be recruited. They were then to be treated with moxonidine (200 mcg). The dose of the drug was increased to 400mcg daily. Those patients who failed to have a satisfactory response to that dose were then randomised to one of the three combinations. This was despite the fact that the data sheet suggested the dose could be increased further to 600mcg if the response was unsatisfactory after three weeks of 400mcg of moxonidine. The company was seeking a total of about 140 patients to be randomised to the three combinations such that approximately 85% of subjects recruited would not actually be involved in answering the main question of the study.

The Solvay researcher was not able to provide satisfactory explanations as to why moxonidine was not increased to its full dose before moving on to a combination of antihypertensive treatments. Further, the researcher was not able to satisfactorily explain why, despite claiming that this drug had been widely used in Europe, there was no information on combination treatment with moxonidine. The researcher was unable to convince the research ethics committee that the combination of antihypertensives with moxonidine was an appropriate therapeutic step in patients who did not respond to moxonidine alone, rather than using a different antihypertensive drug as current guidelines in hypertensive management might suggest.

In writing to Solvay attention was drawn to Clauses 10.2 and 18.1 of the Code.

RESPONSE

Solvay submitted that the study was an international project with a total target of 1,200 patients, of whom 200 were to be recruited in Holland and the remainder from this country. The study had been set up in accordance with the European Guidelines for Good Clinical Practice and with the Declaration of Helsinki. It was within the terms of the marketing authorization but, as matched, blinded add-on treatments were used, the Medicines Control Agency (MCA) had been informed and a copy of the approval letter was provided. It was specified in the protocol that a report of the results of the study and a paper for publication would be prepared.

All study materials were provided to the investigators. If patients were to be continued on Physiotens after completion of the study then it must be prescribed. However, in order to maintain the double-blind requirement of the protocol, supplies of continuation add-on medication would be provided until the study was completed. As study medication was provided free to the investigators, the concern of the ethics committee that the aim of the study was to recruit investigators to "prescribe moxonidine to 1,000 patients" was unwarranted.

Payment to the investigators was £400 per completed case record form. This covered a total of seven assessments. The time spent on each assessment would vary but the minimum was measurement and recording of standing/sitting blood pressure and heart rate, recording any unwanted effects and concurrent medication and dispensing/reconciling study medication. Additionally the investigators must allow sufficient time for routine monitoring procedures. The British Medical Association's suggested fees were £116-150 per hour and the payment for this study was equivalent to about 3.5 hours work (half an hour per assessment) which was well within the guidelines.

The protocol clearly stated the study objectives which, in summary, were to provide data on the use of add-on antihypertensive medication to patients who had *not* responded to moxonidine and to compare the effects of combinations with different classes of antihypertensive in terms of efficacy and tolerability.

The design chosen closely followed normal clinical practice and addressed the clinically relevant question of what course of action should be taken if a patient failed to respond to moxonidine as a single agent. Failure to achieve an adequate response with a single drug was a common difficulty and, despite the view of the ethics

committee, many clinicians preferred to add a second agent. The British Hypertension Society guidelines endorsed this by suggesting that beta-blockers could be used with a thiazide when not effective alone. There were of course a number of combination antihypertensive products on the market which could aid compliance in these cases. Clinicians would not necessarily dose to the maximum permissible level with a single agent as side-effects were usually dose related. Whilst the maximum dosage of moxonidine was 600mcg/day, Solvay knew from experience that most patients would respond to 200 or 400mcg/day. To have allowed an increase to the maximum would have entailed prolongation of the study by a further month and would probably not have achieved a markedly greater response rate. In any case, this would have required even more patients to be entered.

In order to obtain adequate numbers of patients to answer the main question of the study, it was estimated that 1200 patients must be recruited into the first phase. The primary criterion for inclusion into the double blind phase was failure to respond adequately to moxonidine. These patients comprised the group for whom such combinations were relevant.

To date the only trial of moxonidine in combination was with hydrochlorothiazide. If there were substantial data relating to all of the combinations in the study, there would be little point in undertaking it. Not all questions could be addressed during drug development and priorities had to be set.

The study did coincide with the launch of Physiotens in the UK, but it was launched in September 1996 with a small specialist field force to hospital specialists only. The launch to general practitioners would take place in late 1997. The study would not complete and be reported before mid-1998; Solvay would have preferred to have these data prior to this.

The inclusion criteria allowed recruitment of patients on antihypertensive treatment which would be discontinued before entry. However, it was not Solvay's intention that patients who were satisfactorily controlled should be included. Solvay had assured several ethics committees in writing that only newly diagnosed patients or patients whose blood pressure was inadequately controlled or who were suffering tolerability problems with previous medication should be included.

Solvay was confident that the study had been properly designed. It could not be considered as disguised promotion and was not in breach of Clause 10.2 of the Code. In the past the Panel had recorded that this was the only section of the Code which was relevant to clinical assessments. The fees paid to the investigators were justified by the work required and could not be considered as inducements to prescribe Physiotens.

In response to a request from the Panel for further information, Solvay explained that it had assumed an 85% response rate and a 10% dropout rate during each phase of the study (placebo run-in, moxonidine monotherapy and double blind combination). Using these assumptions it was necessary to recruit 1180 patients into the study so that the number completing the double-blind phase was the 129 needed to reach the designated statistical power to answer the questions addressed.

Solvay submitted that the inclusion criteria in the majority of its studies with moxonidine had been very similar to those for this study ie mild to moderate essential hypertension with no stipulation regarding new diagnosis or success/failure to previous treatments. The selection of newly diagnosed patients who were not responding or tolerating their current antihypertensive medication had become an important issue for a number of ethics committees, whose view was that well controlled patients should not be taken off their medication simply to take part in a study. Solvay agreed that this was a valid point and had, therefore, taken it as a general policy even though it was not part of the study inclusion criteria.

PANEL RULING

The Panel noted that the study had been approved by the MCA in relation to trials using products for which product licences had been granted.

The Panel noted that the only requirement in the Code relating to clinical trials and the like was Clause 10.2 which required that studies must not be disguised promotion. The Panel noted that the study in question was being conducted at the time when Physiotens had just become available to hospital specialists. Any such study would inevitably have some promotional impact.

The Panel examined the study documentation and noted that for meaningful results to be achieved 129 hypertensive patients, uncontrolled on moxonidine, were required to complete the study. To achieve this number of patients 1200 had to be recruited in the first place and treated with moxonidine. The Panel accepted that this was a high "wastage" level of patients but considered that the study was being conducted in an attempt to answer valid scientific questions.

The Panel was particularly concerned about the exclusion criteria of the study as these did not include hypertensive patients adequately controlled on other antihypertensive medication. The Panel queried whether it was acceptable to enter such patients in the study as for the first four weeks patients were given placebo. The Panel considered that the inclusion/exclusion criteria might lead to patients adequately controlled on other antihypertensive therapy being unnecessarily changed to moxonidine therapy with the potential for this treatment to be continued beyond the trial period. The Panel noted that it was neither Solvay's intention, nor the company's general policy, to include in the trial patients who were satisfactorily controlled. The Panel considered that this point should have been clearly stipulated in the documentation. The company would be well advised to point this out when recruiting doctors.

The Panel considered that the payments were reasonable given that the British Medical Association suggested fee for participation in clinical trials was, according to the Authority's information, £121 per hour and pro rata.

Despite its concerns about the recruitment of the study population, the Panel considered that the trial was not promotional in nature and ruled no breach of the Code.

Complaint received **30 October 1996**

Case completed **9 January 1997**

CIBA v SEARLE

Arthrotec 75 journal outsert

Ciba complained about a journal outsert for Arthrotec 75 (diclofenac 75mg/misoprostol 200 mcg) issued by Searle. It was alleged that a claim "Significantly fewer gastroduodenal ulcers compared with diclofenac SR" was not a balanced view of the study findings and that a claim "As effective as diclofenac 75mg SR" was wrongly referenced.

The Panel considered that the methodological criticisms of the study made by Ciba had been adequately addressed by Searle. The study did show in all but one of the endoscopic assessments that there had been a significant difference in incidence in favour of Arthrotec 75 and in the other assessment there had been no significant difference between the treatments although there was a trend in favour of Arthrotec 75. No breach of the Code was ruled. The claim in question was referenced to data on file (it was the same study as referred to above). The Panel noted that there was no obligation under the Code to give a reference other than when referring to published studies. The error in giving the wrong study report number was unfortunate but the Panel did not consider that it amounted to a breach of the Code.

Ciba Pharmaceuticals complained about the promotion of Arthrotec by Searle in a promotional item (AR: GPOS75L 596 May 1996) which Ciba believed to be a detail aid. Searle explained that the material at issue was actually a journal advertisement bound as an outsert to GP, 5 July 1996. There were two allegations.

1 "Significantly fewer gastroduodenal ulcers compared with diclofenac SR"

COMPLAINT

This statement was referenced to a single study. Ciba alleged that the statement implied that all ulceration seen during the study was caused by diclofenac. However, in the study gastroscopy was only carried out at the end of the treatment period and no baseline pre-treatment endoscopy was performed. In these circumstances it was not possible to exclude differences in ulceration caused by factors other than NSAID-exposure. As the study results could be significantly compromised by this methodological flaw, Ciba alleged that it could not support a statement that a real difference existed between the two treatments.

As a secondary consideration, the document supplied by Searle contained no information on the grade of ulcers present following treatment, only the number present. Other information presented in the results suggested that grade may be an important correlate. For example, the study results showed that there were no between-treatment differences in the number of bleeding lesions and there were in fact no differences in the number of withdrawals due to unwanted effects. These findings could be explained by the fact that the ulcers seen in the diclofenac SR group were of a lower, less severe, less clinically significant grade than those found in the Arthrotec group.

Ciba alleged that a balanced view of the study findings had not been provided by the use of this statement and there was therefore a breach of 7.2 of the Code.

RESPONSE

Searle believed that the statement was entirely consistent with the product licence for Arthrotec 75mg SR since both products (Arthrotec 75 and diclofenac 75mg SR) were used twice a day and provided a total daily dose of 150mg diclofenac. Arthrotec 75 contained, in addition, misoprostol "indicated for the prophylaxis of NSAID induced gastric and duodenal ulceration" (Arthrotec SPC). If a medicine was licensed to prevent ulcers it was implicit in the product licence that patients who received the medicine had been shown to develop fewer ulcers than those who did not.

The statement was supported by a large clinical trial which demonstrated a clear difference in ulceration rates after three months treatment with Arthrotec (6.7%) or diclofenac SR (19.4%), (p=0.001). This analysis used a definition of ulcer which was of a mucosal lesion with unequivocal depth regardless of size. When the analysis was performed on ulcers of 5mm or more the rates were 5.2% and 14.8% and the significance was still p=0.001.

The study was a large randomised controlled study conducted for registration purposes at 51 hospital sites in 10 countries. The study design was therefore reviewed and approved by a large number of regulatory authorities and local research ethics committees, and the results were accepted for presentation at the meeting of the European League Against Rheumatism (EULAR) in Madrid in October 1996.

Ciba described the study as suffering from a 'methodological flaw' because there was no pre-treatment endoscopy. Searle strongly refuted that. Ciba was arguing that the differences between treatment groups could have arisen because of a chance imbalance between the groups which was not detected because there was no baseline endoscopy. In any randomised controlled trial there was, of course, a possibility that differences between treatments had occurred by chance. In this study the probability of this had been quantified as less than 1 in a thousand.

Pre-treatment endoscopies were necessary in small studies of short duration ie Phase I/II studies of 1-2 weeks duration. An ulcer present at baseline could still be present two weeks later and bias the results. When over five hundred patients were investigated, as in this study, baseline endoscopy was unnecessary because of the power of randomisation. Looking at the baseline characteristics, it could be seen that the groups were remarkably well matched, and where there was a numeric difference in the percentage of patients with risk factors (e.g. history of ulcer or GI haemorrhage) the factor was over represented in the Arthrotec group, thereby

increasing the likelihood of ulceration in that group rather than in the diclofenac 75mg SR group. Searle also knew that risk for ulceration due to *H pylori* was evenly distributed in both treatment groups. It was in fact a methodological flaw to include a baseline endoscopy in a study of this magnitude because that resulted in exclusion of patients susceptible to NSAID damage and consequently a biased sample, unrepresentative of the population of NSAID users. This study design thus represented an advance on previous methodology.

Ciba pointed out that there was no information on 'grade' of ulcer in the report. Searle was not aware of any grading scheme for ulcers that had been shown to correlate with clinical sequelae. Searle and others routinely collected information on size only. Ciba's suggestion that ulcers on diclofenac were less clinically significant than on Arthrotec was pure speculation. The clinical significance of the GI damage was highlighted by the haemoglobin fall with diclofenac which was approximately double that of Arthrotec.

Searle did not see how the bullet points could be construed as misleading. They were a true reflection of a large, robust, clinical trial in which Arthrotec came out equal to or ahead of diclofenac on every parameter measured.

PANEL RULING

The Panel noted that the statement was referenced to a study which had compared Arthrotec 75 and diclofenac 75mg SR in over 500 patients with arthritis. Endoscopy had been performed at the end of this study, after 12 weeks treatment, in over 400 patients. In all but one of the endoscopic assessments there had been a significant difference in incidence in favour of Arthrotec 75. In the remaining assessment there was no significant difference between treatments although there was a trend in favour of Arthrotec 75. The Panel considered that the methodological criticisms made of this study, these being the absence of pre-treatment endoscopy and the lack of information on grade of ulcers, had been adequately answered by Searle in its response and could not be considered sufficient to invalidate the conclusions of the study. The Panel also noted Searle's submission that the statement was consistent with the product licence for Arthrotec 75.

The Panel did not consider that the statement was misleading and ruled that there had been no breach of Clause 7.2 of the Code.

2 "As effective as diclofenac 75mg SR"

COMPLAINT

Ciba pointed out that the Study Report NN2-95-06-349 used to support this statement was not relevant as the comparator used was not stated to be a sustained-release formulation of diclofenac. There were other formulations of Voltarol available, also containing 75mg of diclofenac, which were not sustained release in nature. The statement as it stood was therefore in breach of 7.2 of the Code.

Ciba said that Searle had admitted that the wrong reference was used and had agreed to change the material eventually but not to withdraw it in the meantime. In Ciba's view, this meant that material containing incorrect information would continue to be in circulation and so would continue to be in breach of the Code which was an unacceptable state of affairs.

RESPONSE

Searle noted that Ciba did not dispute the veracity of the statement which was again supported by the above study. Although not required by the Code, this statement was correctly referenced to "data on file". However, the reference numbers which followed, and which were for Searle's internal use to allow different sections of the data-on-file to be identified, inadvertently became transposed. Searle accept that this was an error and had promised Ciba that it would be corrected in future material. Searle did not see how it was possible to accede to Ciba's request to withdraw the material when it was a one-off journal advertisement and a minor referencing error. In addition, since discovery of the error, Searle's medical information department had sent out both references together in response to any enquiry.

Searle therefore did not accept that this statement breached Clause 7.2 because the information which was conveyed in the statement was accurate irrespective of any error in the footnote numbering.

PANEL RULING

The Panel noted that the claim was referenced to "data on file" followed by a reference number for internal use only which related to different sections of Searle's in-house data. There was of course no obligation to provide a reference at all in such circumstances as references were only obligatory under Clause 7.5 of the Code when referring to published studies. Clearly, the error was unfortunate but the Panel did not consider that it amounted to a breach of the Code. No breach of Clause 7.2 was ruled.

The Panel noted that Searle's medical information department had sent out both references together since discovering the error. The Panel considered that Searle should send on both references to anybody who had enquired prior to the mistake being known.

Complaint received	**14 November 1996**
Case completed	**13 January 1997**

CASE AUTH/476/11/96

PASTEUR MÉRIEUX MSD v SMITHKLINE BEECHAM

Havrix mailing

Pasteur Mérieux MSD complained about a mailing for Havrix issued by SmithKline Beecham. The mailing consisted of a "Dear Doctor" letter, a one page sheet comparing Havrix with the Pasteur Mérieux MSD hepatitis A vaccine, Avaxim, and a reply paid card offering a travel medicine handbook or a mousepad.

The Panel ruled that a claim "Protect all your patients from hepatitis A in one easy dose" was all embracing and in breach of the Code.

No breach was ruled regarding allegations that the non proprietary name was not adjacent to the most prominent display of the brand name in the "Dear Doctor" letter and on the one page sheet. On the "Dear Doctor" letter, however, the non-proprietary name was not the correct size as it appeared in a type size smaller than 10 point bold and a breach was ruled.

The statement "Proven protection" followed by a tick for Havrix and a cross for the Pasteur Mérieux MSD product was considered by the Panel to be disparaging of Avaxim and misleading as the word "proven" was considered to be too strong. On appeal by SmithKline Beecham, the Appeal Board upheld the ruling that it disparaged Avaxim and also ruled the statement to be misleading because the data used to support the claim related only to children and used a different formulation and dosage schedule to that currently used.

No breach was ruled with regard to the failure to reference a statement as the statement did not refer to a published study and a reference was therefore not required. No breach was ruled regarding a statement about shelf life which was considered to be a statement of fact. The Panel accepted that SmithKline Beecham had data to substantiate a statement referring to clinical experience. The use of the superlative "most" in the claim "most widely used" was ruled to be acceptable. A claim referring to use of Havrix in children under 16 was ruled not to be unreasonable as a version of Havrix could be used in such patients.

Pasteur Mérieux MSD Ltd complained about the promotion of Havrix by SmithKline Beecham Pharmaceuticals UK.

The material at issue was a mailing consisting of a "Dear Doctor" letter, a one page sheet headed "The Success of Havrix" and a reply paid card requesting certain information and offering a complimentary gift of a travel medicine handbook or a mousepad. There were several allegations which were considered as follows:

"Dear Doctor" letter

1 Claim "Protect all your patients from hepatitis A in one easy dose!"

This claim appeared as the heading to the "Dear Doctor" letter.

COMPLAINT

Pasteur Mérieux MSD alleged that the claim was not substantiated in the letter and nor by the only reference cited in the mailing, on the one page sheet headed "The Success of Havrix", which was a study by Innis B *et al.* This study did not demonstrate that the vaccine gave 100% protection against hepatitis A as cases of hepatitis A were reported. The claim was alleged to be inaccurate and all embracing in breach of Clauses 7.2 and 7.8 of the Code.

RESPONSE

SmithKline Beecham submitted that the claim referred to the fact that Havrix was available as a monodose for both adults and children. It was clearly supported by the text of the letter. One dose of the Monodose presentation provided protection against hepatitis A for at least one year. Thus all of a doctor's patients could be protected against hepatitis A with one dose of Havrix. To suggest that it was a claim of 100% efficacy appeared to be a rather contrived interpretation.

PANEL RULING

The Panel considered that the claim would be interpreted as claiming that Havrix was effective in all patients. No vaccine was 100% effective in all patients. The Panel therefore decided that the claim was all embracing and ruled a breach of Clause 7.8 of the Code.

2 Size and positioning of the non-proprietary name

COMPLAINT

Pasteur Mérieux MSD alleged that the non-proprietary names in the "Dear Doctor" letter did not appear in a typesize not less than 10 point bold as required by the Code. Pasteur Mérieux MSD also questioned whether the most prominent display of the brand names was at the bottom of the letter since the name, Havrix Monodose, appeared in bold at least six times in the body of the letter.

RESPONSE

SmithKline Beecham accepted that due to photographic reduction of the Havrix logo, the non-proprietary name was smaller than required. This oversight had been noted and appropriate action taken. The company submitted that the most prominent mention of the brand name was clearly the logo at the bottom of the letter.

PANEL RULING

The Panel noted that the non-proprietary name was smaller than the requisite 10 point bold as acknowledged by the company and therefore ruled a breach of Clause 4.1 of the Code. It considered that the most prominent display of the brand names on the letter was at the bottom of the letter which had the non-proprietary names

immediately adjacent and ruled that there was no breach in that regard.

* * *

The following seven allegations referred to the sheet headed "The Success of Havrix" which listed seven product benefits. For each benefit listed a tick appeared in the column marked "Havrix" and a cross appeared in the column marked "hepatitis A vaccine (Pasteur Mérieux)". Pasteur Mérieux MSD complained that the sheet appeared to have been designed specifically to disparage Avaxim rather than give factual information. Many of the benefits appeared to be unsubstantiated and have no special merit. Certain benefit statements were questioned and the specific allegations were as follows:

3 " "Green Book" - recommended needle gauge for intramuscular injections"

The statement was followed by a tick in the Havrix box and a cross in the hepatitis A vaccine (Pasteur Merieux) box.

COMPLAINT

Pasteur Mérieux MSD alleged that the statement " "Green Book" - recommended needle gauge for intramuscular injections" was not an adequate reference in breach of Clause 7.5. On the assumption that the "Green Book" was a reference to the book "Immunisation against Infectious Disease (HMSO)", the latest edition indicated in a diagram that a 25 gauge needle, such as was incorporated with Pasteur Mérieux MSD's product, Avaxim, was appropriate for intramuscular administration.

RESPONSE

SmithKline Beecham pointed out that the "Green Book" was the accepted UK reference for vaccination and as such was an adequate reference. It was distributed to all practitioners in the UK.

With regard to the recommended needle size, it was true that the diagram showed a 25 gauge needle being used for intramuscular administration. However, this diagram's purpose appeared to be to demonstrate different needle orientations for entering various compartments and was clearly labelled as such. The text clearly stated that "For deep subcutaneous or intramuscular immunisation in infants, a 23 or 25G needle should be used. For adults a 23G needle is recommended." Thus the needle size for Havrix was within the recommendations. The 25G needle used for Avaxim was not as this product was only licensed for adults.

PANEL RULING

The Panel noted that in this instance there was no need to reference the statement. Clause 7.5 of the Code required that a reference was given when referring to a published study. No breach of Clause 7.5 was ruled. The Panel considered that the "Green Book" was confusing in this area. The diagram which was labelled "Needle orientation for intradermal, subcutaneous and intramuscular injections" did show a 25G a needle for an intramuscular injection whereas the text, under the heading "Administration", stated that "For deep subcutaneous or intramuscular immunisation in infants, a 23 or 25G needle should be used. For adults, a 23G needle is recommended". The Panel considered that it was true to say that the 23G needle was recommended for intramuscular injections. Avaxim was supplied with a 25G needle. The Panel therefore ruled no breach of Code.

4 "Proven protection"

The sheet gave a tick in the Havrix box and a cross in the hepatitis A vaccine (Pasteur Merieux) box.

COMPLAINT

Pasteur Mérieux MSD alleged that the claim "Proven protection" implied that Avaxim did not provide protection against hepatitis A. This outrageous implication was in breach of Clause 8.1. Avaxim was a licensed vaccine and approved for use in protection against hepatitis A. The reference given in the material (the study by Innis *et al)* was inappropriate as it used a vaccine that was neither the current formulation of Havrix Monodose nor Havrix Junior Monodose and used different dosage schedules to those currently licensed for either Havrix or Avaxim. The study only included children and only assessed the response to one hepatitis A vaccine. It was misleading to imply that the reference supported a comparison between Havrix and any other hepatitis A vaccine.

RESPONSE

SmithKline Beecham said that the claim "Proven protection" applied to the fact that Havrix had been proven in a clinical study involving over 40, 000 children to protect against clinical hepatitis A disease. No such data existed for Avaxim. The statement did not detract from the fact that Avaxim was a licensed product in the UK. Vaccines were frequently licensed on their ability to evoke an antibody response in vaccinees, efficacy being correlated to a nominal protective level. The ultimate test of a vaccine was whether or not it could protect humans from clinical disease. True protective efficacy of a vaccine could only be established in an internationally accepted manner. This involved conducting suitably designed clinical studies, providing data to prove that administration of the vaccine did protect vaccinees from the disease. Havrix had been clinically proven to protect against hepatitis A infections in humans, Avaxim had not. This was a factual statement which allowed physicians to make an informed choice.

SmithKline Beecham accepted that the dose differed from the current schedules for Havrix Monodose and Havrix Junior Monodose. The study proved that the antigen protected against disease. The group in which the study was performed was irrelevant to the statement in that protection with Havrix had been proven. The material compared Havrix and Pasteur Mérieux MSD's hepatitis A vaccine in terms of whether or not they had certain attributes. There was no implication that there was any direct clinical study comparing the two vaccines.

PANEL RULING

The Panel noted that the cited reference only referred to children. Some readers would assume that the reference compared Havrix with Avaxim which was not so.

In the Panel's view, the implication of the claim and the tick for Havrix and the cross for hepatitis A vaccine (Pasteur Merieux) was that Havrix was proven to protect against hepatitis A and Avaxim was not. Both products were licensed for the identical indication of active immunisation against infection caused by hepatitis A virus. The Panel considered that the use of the word proven in the claim "Proven protection" was too strong given that the vaccine would not be successful in 100% of patients. The Panel considered the claim was misleading and disparaging of Avaxim and therefore ruled breaches of Clauses 7.2 and 8.1 of the Code.

APPEAL BY SMITHKLINE BEECHAM

SmithKline Beecham said that the claim in question was one statement from a piece which showed points of differentiation between two brands of hepatitis A vaccine, Havrix and Pasteur Mérieux MSD's hepatitis A vaccine (Avaxim). In reaching its decision, the Panel appeared to have considered that there were two issues which were pertinent.

Firstly that both products were licensed for the identical indication of active immunisation against infection caused by hepatitis A virus, and secondly, that the use of the word proven in the claim "Proven protection" was too strong given that the vaccine would not be successful in 100% of patients.

While it was true that both Havrix and Avaxim had the same licensed indication, it was important to be aware that vaccines were generally granted a product licence based on their ability to produce an immunological response, most frequently production of each specific antibody. Efficacy was then considered in terms of "seroprotection", defined as the percentage of patients with antibody levels above a cut-off value which had been determined from animal models.

The ability of a vaccine to confer true protection against a disease could only be studied in humans, using a suitably powered trial. Such a trial had been carried out with Havrix (Innis *et al*) but not with Avaxim. SmithKline Beecham said that this view was supported by Pasteur Mérieux in a recent paper (Vidor *et al* 1996) which said that "No efficacy trial has been conducted with the Pasteur Mérieux vaccine. However, there are several arguments in favor of its protective efficacy". It was accepted that Havrix had been shown to protect humans and that Avaxim had not. The paper then listed arguments as to why Avaxim should be protective, confirming that this was a clinically relevant issue.

With regard to the use of proven being too strong given that the vaccine would not be successful in 100% of patients, the company submitted 100% effectiveness was not required before something could be said to be proven. There were many examples of proven treatments that were not 100% effective.

In summary, the statement "Proven protection" was used to demonstrate a specific difference between Havrix and Avaxim. The study carried out by Innes *et al* in over 40,000 subjects proved beyond reasonable doubt that Havrix could confer protection against hepatitis A infections in humans. There was no such data for Avaxim.

The company pointed out that promotional material was assumed to refer to the clinical situation unless otherwise informed. The claim "Proven protection" referred to clinical data in humans and there was no such data for Avaxim.

APPEAL BOARD RULING

The Appeal Board noted that there was a difference in the way vaccines were licensed, compared to other medicines. This difference might not be known to readers of the material in question who would take it as meaning that Avaxim would not give protection from hepatitis A. Readers would not appreciate that, taking into account the way vaccines were licensed, it was reasonable for Avaxim as a licensed hepatitis A vaccine not, as yet, to have been shown in clinical studies to give protection from hepatitis A. The Appeal Board upheld the Panel's view that the material was disparaging of Avaxim and ruled a breach of Clause 8.1 of the Code.

The Appeal Board did not agree with the Panel's view that the term "Proven protection" was unacceptable because the vaccine would not be successful in 100% of patients. The Appeal Board did consider, however, that the claim was misleading in relation to Havrix, given that the data related to a study on children with a different product and a different dosage schedule to the currently available product Havrix Monodose. The Appeal Board therefore ruled a breach of Clause 7.2 of the Code.

The appeal therefore failed.

5 "Three-year shelf life"

The sheet gave a tick in the Havrix box and a cross in the hepatitis A vaccine (Pasteur Merieux) box.

COMPLAINT

Pasteur Mérieux MSD alleged that the statement was in breach of Clause 7.8 of the Code as the fact that Havrix had a three year shelf life and that Avaxim did not had no special merit. The important feature for a user when supplied with a pharmaceutical product was the remaining shelf life of the particular batch supplied.

RESPONSE

SmithKline Beecham said that the statement was a statement of fact which might be of benefit to practitioners if they carried stocks of vaccines.

PANEL RULING

The Panel accepted that the statement was a statement of fact. Havrix had a three year shelf life and Avaxim had a two year shelf life. The Panel therefore ruled no breach of the Code.

6 "Benefits of clinical experience in over 15 million patients worldwide"

The sheet gave a tick in the Havrix box and a cross in the hepatitis A vaccine (Pasteur Merieux) box.

COMPLAINT

Pasteur Mérieux MSD alleged that it was claimed that Havrix had the benefit of clinical experience in over 15 million patients worldwide and that Avaxim did not. The accuracy of these two assertions was neither referenced nor otherwise supported. A breach of Clause 7.3 was alleged.

RESPONSE

SmithKline Beecham submitted that the statement did not require referencing as it did not relate to a published study. It was supported by data and therefore not in breach of the Code. With regard to the clinical relevance of the statement, vaccines were generally safe products given to healthy individuals. However, previous experience had shown that only after extensive experience with a vaccine had some rare side effects been observed. Indeed this had led to the withdrawal of products. The level of experience with Avaxim therefore had clinical relevance.

Following a request for further information, the company provided sales figures and an IMS Mediplus analysis of compliance with hepatitis A vaccination to support the statement. The data was a mixture of data from vaccination with Havrix original and vaccination with Havrix monodose. The number of patients who had received at least one dose of Havrix was over 15 million.

PANEL RULING

The Panel noted that the data provided by the company related to sales. It demonstrated that more than 15 million patients worldwide had received Havrix. The statement referred to clinical experience which might be interpreted as meaning more than simply administering a dose of Havrix. The data did show, however, that there was substantial experience of the use of Havrix and the Panel considered that that was how the statement would be interpreted by the audience. Given the circumstances the Panel ruled no breach of Clause 7.3 of the Code.

7 "Most widely used hepatitis A vaccine"

The sheet gave a tick in the Havrix box and a cross in the hepatitis A vaccine (Pasteur Merieux) box.

COMPLAINT

Pasteur Mérieux MSD alleged that the claim was exaggerated and used a superlative in breach of Clause 7.8. There was no special merit in such a claim which related to the duration of availablility of a product on the market and not necessarily merit. It was only recently that the monopoly of Havrix had been broken and that customers had a choice of hepatitis A vaccines.

RESPONSE

SmithKline Beecham said that the claim could be substantiated and referred to the supplementary information to Clause 7.8 which allowed superlatives to be used in certain circumstances. These being simple statements of fact which could be very clearly demonstrated.

Following a request for further information, the company referred to IMS sales data to support the claim. Havrix was the only licensed hepatitis A vaccine in the UK until recently.

PANEL RULING

The Panel accepted that this was an instance whereby a superlative could be used as the issue was one of fact and not one of opinion. Given the data it was acceptable to claim that Havrix was the most widely used hepatitis A vaccine. No breach of Clause 7.8 was ruled.

8 Position of non-proprietary name

COMPLAINT

Pasteur Mérieux MSD alleged that the use of the name "Havrix" at the top of the sheet should have the non-proprietary name adjacent to it as this was the most prominent display of the brand name being in the largest font appearing at the top of the sheet. A breach of Clause 4.1 was alleged.

RESPONSE

SmithKline Beecham said that although the name "Havrix" appeared at the top of the sheet the most obvious mention of the brand name was that at the bottom showing the logo. This occupied more space than the previous mention and was more prominent.

PANEL RULING

The Panel considered that it was arguable as to which presentation of the brand name was the most prominent and considered that it would be acceptable for the non-proprietary name to appear either immediately adjacent to the heading at the top of the page or at the bottom where the names Havrix Monodose and Havrix Junior Monodose appeared in logo form with the non-proprietary name immediately adjacent to the brand names. The Panel ruled no breach of the Code.

9 "Use in children under 16"

The sheet gave a tick in the Havrix box and a cross in the hepatitis A vaccine (Pasteur Merieux) box.

COMPLAINT

Pasteur Mérieux MSD accepted that Avaxim did not have a licence for use in those under 16 years of age. It was not made clear in this claim as to which product "Havrix" referred. The current hepatitis A vaccines marketed by SmithKline Beecham would appear to be Havrix Junior Monodose which was licensed for those under 16 years of age and Havrix Monodose which was licensed for adults and those aged 16 years and over. Thus the use in children under 16 could only apply to Havrix Junior

Monodose. The claim could not apply to Havrix Monodose. A breach of Clause 3.2 of the Code was alleged.

RESPONSE

SmithKline Beecham pointed out that the material related to the Havrix range which would include both the Monodose and the Junior Monodose. The statement was factual and not in breach of Clause 3.2.

PANEL RULING

The Panel accepted that the material was promoting Havrix in general terms. It was not unreasonable to refer to the use in children under 16 as a version of Havrix could be used in such patients. The Panel therefore ruled no breach of Clause 3.2 of the Code.

* * *

10 Mousepad

COMPLAINT

Pasteur Merieux MSD alleged that the document "The Success of Havrix", the subject of allegations 3 - 9 inclusive, was reproduced on a mousepad offered as a giveaway in the mailing. It therefore requested that not only should the mousepad be withdrawn but also that any that had been distributed be recalled and a letter of retraction sent to all those who had received the mailing.

RESPONSE

SmithKline Beecham said that it had yet to receive any stock of the mousepads as it was awaiting an indication of demand prior to printing. However the text would be identical to the piece "The Success of Havrix" with the addition of prescribing information on the right hand side.

PANEL RULING

The Panel noted that SmithKline Beecham had not yet distributed any mousepads. The Panel noted that rulings of breaches of the Code with regard to the document "The Success of Havrix" would also apply to the mousepad.

Complaint received **15 November 1996**

Case completed **4 February 1997**

CASE AUTH/477/11/96

CONSULTANT PHYSICIAN v RECKITT & COLMAN

Fybozest advertisement

A consultant physician complained about a journal advertisement for Fybozest issued by Reckitt & Colman. The complainant said that it was unclear whether the claimed reduction of cholesterol when Fybozest was used first line with diet was due to the Fybozest or the diet. In addition, as the supporting reference was "submitted for publication" there was no indication as to whether it had been peer reviewed or as to the quality of the journal in which it would be published.

The Panel noted that all claims in promotional material had to be capable of substantiation. Data used for substantiation did not have to be limited to published papers in peer reviewed journals. The Panel considered that the claim was reasonable and was substantiated by the short unpublished paper provided. No breach was ruled.

On appeal by the complainant, Reckitt & Colman supplied a more detailed version of the original paper as it was now known that the short paper had not been accepted for publication. The Appeal Board identified flaws and inconsistencies in the different versions of the data provided. The Appeal Board considered that the claim in question was misleading and had not been substantiated. Breaches of the Code were ruled.

A consultant physician complained about a journal advertisement for Fybozest (ispaghula husk) issued by Reckitt & Colman Products Limited. The advertisement appeared in Hospital Doctor and contained the claim for Fybozest "It quite simply lowers cholesterol, by up to 10% when used first line with diet". The cited reference was "submitted for publication".

COMPLAINT

The complainant said that it might be that ispaghula would lower cholesterol but he did not think it was reasonable for Reckitt & Colman to have such a broad based advertisement claiming 10% lowering of cholesterol when used first line with diet. It was not clear whether it was the ispaghula or the diet that was lowering this. The complainant said that the cited reference was not published. It had not been through peer review and it was therefore not clear whether or not the paper concerned would be published. The advertisement did not give any indication therefore of the quality of the journal in which the paper was to be published.

In considering the matter, Reckitt & Colman was asked to bear in mind the requirements of Clauses 7.2 and 7.3 of the Code.

RESPONSE

Reckitt & Colman submitted a product monograph for Fybozest and, following a request for further information, a draft of a paper which had been submitted to the British Medical Journal (BMJ) for publication and which was undergoing peer review. The paper reported the results of a 24 week large scale, double-blind, placebo controlled study which had examined the use of ispaghula husk and diet on cholesterol levels in hypercholesterolaemic patients. The study demonstrated that ispaghula husk could produce a significant reduction in LDL-cholesterol

and total cholesterol in patients with mild to moderate hypercholesterolaemia already taking a cholesterol lowering diet.

PANEL RULING

The Panel noted that references in promotional material did not have to be limited to papers published in peer reviewed journals. It was permissible to reference material to data on file including papers submitted for publication. The important point was that everything in promotional material had to be capable of substantiation and that such substantiation was provided on request. The quality of the data, not where it had appeared, was the basis of judgements regarding substantiation.

The Panel noted that, according to the prescribing information contained in the product monograph, Fybozest was indicated for "Reduction of mild to moderately elevated total serum cholesterol levels (6.5-7.8mmol/l), and for maintenance of lowered levels thereafter. To be used in conjunction with dietary modification".

The Panel considered that the draft report of the study provided by Reckitt & Colman supported the claim "Fybozest ... It quite simply lowers cholesterol, by up to 10% when used first line with diet". It was clear from the results that the lipid lowering effect observed was due to the effect of the ispaghula husk plus diet and not the diet alone. In the light of the study results the claim was reasonable. The Panel therefore ruled no breach of Clause 7.2 of the Code.

The Panel noted that the manuscript had not yet been accepted for publication but that Reckitt & Colman was prepared to make it available to enquirers following a request for substantiation thus fulfilling the requirements of Clause 7.3 which stated that any claim must be capable of substantiation. The Panel ruled no breach of the Code in this regard.

APPEAL BY THE COMPLAINANT

The complainant said that the whole point of a placebo controlled trial was to adjust for baseline shifts related to taking part in a study. That there were substantial shifts related to taking part in the study was clearly shown by the figure included in the manuscript draft (supplied to him by the Authority).

The differences that mattered in this situation were those between placebo and treatment. It was not clear that this was what was being referred to in the advertising and even with the manuscript draft, the complainant was still not clear about the comparison.

As a manuscript submitted to a major journal for publication it surprised the complainant that it included no statistical analysis at all and no p-values. It was stated that the falls on treatment were "significantly greater" but no statistical evidence was provided.

Advertising should say that a cholesterol fall of a certain percentage was seen after diet, rather than with diet. It was important that the product used to lower cholesterol had an effect additional to the dietary input.

As a minor matter, but related to the difficulty of confidentiality, the complainant believed that if data was to be used in advertising then it had to be in the public domain, or at least as a minimum, within limited circulation to those who enquired about it. It seemed unacceptable that claims could be made in advertising when the data was not available to individuals being targeted by that advertising.

Furthermore, the complainant had written twice to Reckitt & Colman asking if he could have sight of the information that the Authority had sent him and had had no reply. The complainant had telephoned Reckitt & Colman once where the response from the medical department was that the information was confidential.

RESPONSE FROM RECKITT & COLMAN

Reckitt & Colman addressed in turn each of the issues raised by the complainant.

"The whole point of a placebo controlled trial was to adjust for baseline shifts related to taking part in the study"

Reckitt & Colman agreed with the complainant's comment and in the design of the first 12 weeks' treatment phase of its clinical studies with Fybozest this was taken into consideration. The data showed significant incremental reduction in cholesterol levels on treatment with Fybozest and dietary advice over the placebo control group (ie dietary advice only). The design for the 12 week extension study focused on tolerability rather than efficacy and hence there was no placebo control. However, Reckitt & Colman could conclude from the placebo controlled trial that the active ingredient in Fybozest, ispaghula husk, was responsible for a positive additional effect on reducing cholesterol levels over and above the effect which could be reasonably expected from dietary advice alone.

"The differences that mattered in this situation were those between placebo and treatment. It was not clear that this was what was being referred to in the advertising"

Reckitt & Colman submitted that the advertisement for Fybozest in the Hospital Doctor magazine clearly said that Fybozest "quite simply lowers cholesterol by up to 10% when used first line with diet". In this and all other promotional materials produced thus far for Fybozest, Reckitt & Colman had clearly stated that the cholesterol lowering effect observed with the product was in conjunction with dietary modification, not on top of any effect which could be expected from dietary modification alone. This was in line with the licence granted for the product.

"As a manuscript submitted to a major journal for publication it surprised the complainant that it included no statistical analysis at all and no p-values. It was stated that falls on treatment were significantly greater but no statistical evidence was provided"

Reckitt & Colman was aware that the short review paper submitted to the BMJ was not detailed but there was a commercial reason for this. For products covered by patent protection there was no detriment in publishing extensive efficacy and safety data. However, for products which did not enjoy patent protection, such as those based

on ispaghula husk, publishing extensive data allowed competitor companies the opportunity to refer to this data to obtain their own product licences without undertaking their own clinical studies.

Clearly such a situation would not be in Reckitt & Colman's best interest and it therefore chose the BMJ short communication as the optimum publication route. Reckitt & Colman had now heard that the BMJ could not publish the short paper because of the lack of detailed information so, in this instance, the company appeared to have erred on the side of caution. However, a more detailed paper had been drafted by the principal trial investigator a copy of which was supplied. Reckitt & Colman said that the information given in this paper should address all of the complainant's concerns on the lack of statistical analysis and other study details which were not included in the short paper. The principal investigator intended to submit this detailed paper to the BMJ.

"Advertising should say that a cholesterol fall of a certain percentage was seen after diet, rather than with diet. It is important that the agent used to lower cholesterol had an effect additional to the dietary input"

On the first point Reckitt & Colman appreciated that this was the complainant's opinion. The company was bound by the terms of its product licence to make it clear that the two elements of treatment of raised cholesterol, Fybozest and dietary modification, should be used together to obtain optimum effect.

On the second point, Reckitt & Colman submitted that its 12 week efficacy study clearly showed a significant difference between patients treated with Fybozest and diet compared with those treated with placebo (ie diet alone). The combined 24 week study data provided justification for the 10% cholesterol reduction claim for Fybozest in conjunction with diet. Reckitt & Colman did not have the evidence to support a 10% reduction claim on top of diet and its advertising did not make this claim. It was widely accepted that dietary modification was still necessary whenever any cholesterol lowering intervention was indicated. All Reckitt & Colman's advertising clearly advocated the use of Fybozest as an adjunct to diet in line with the cholesterol management recommendations of both the British Hyperlipidaemia Association and the European Atherosclerosis Society. These guidelines were increasingly being used as a basis for developing clinical protocols for the treatment of hyperlipidaemia, particularly within the EC. Reckitt & Colman agreed that a cholesterol lowering agent should have an effect additional to the dietary input and it had shown beyond reasonable doubt that this was the case with Fybozest.

"I had believed that if data was to be used in advertising it had to be in the public domain, or at least as a minimum, within limited circulation to those who enquired about it. It seemed unacceptable that claims could be made in advertising when the data was not available to individuals being targeted by that advertising"

Reckitt & Colman submitted that although this point was not part of the original complaint by the complainant, it entirely agreed that product information should be made available to healthcare professionals and, indeed, copies of the data sheet and product monograph were available to anyone requesting more detailed information on Fybozest. However, due to the BMJ's own strict editorial policy on clinical trial data submitted for publication, Reckitt & Colman had been more circumspect in distributing the BMJ paper itself.

"Furthermore, the complainant had written twice to Reckitt & Colman asking if he could have sight of the information that the Authority had sent him and had had no reply. The complainant had telephoned Reckitt & Colman once where the response from the medical department was that the information was confidential"

Reckitt & Colman submitted that it had received a letter from the complainant followed by a fax from the Authority three days later with a copy of his letter of complaint. The company therefore considered that the most appropriate route for responding to the complainant was through the Authority. Reckitt & Colman had no record of a second letter from the complainant or of his telephone enquiry in the unit which dealt with such requests. Clearly Reckitt & Colman would like to investigate how its systems had failed in this situation and would appreciate a copy of the complainant's second letter and further details of the date, time and point of contact for his telephone call to help it with this.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant said that the data submitted by Reckitt & Colman was poor and did not show what was purported. Used as an adjunct after diet, ispaghula might lower cholesterol by 3% but that required statistical analysis. What the paper showed was that patients all responded to entry into a study, by diet or otherwise, but there was little to suggest any or other than a modest further improvement with ispaghula husk. The complainant addressed his initial points in turn.

"Reckitt & Colman's reply to "the whole point of the placebo controlled trial was to adjust for baseline shifts related to taking part in the study"

The complainant noted that Reckitt & Colman had agreed with the statement and said that in the design of the first 12 week treatment phase of its clinical studies with Fybozest this principle had been taken into consideration. If this was so, the company had completely missed the point of the issue. Its advertising, and to an extent the previous and current manuscript, made conclusions not justified by the data.

The complainant contended that Reckitt & Colman might or might not be able to conclude that ispaghula husk was responsible for a positive additional effect on reducing total cholesterol levels over and above the effect of diet. It was certainly not 10% (which the data did not substantiate even with diet). Whether it was really significant or not was still not answered.

"... quite simply lowers cholesterol by up to 10% when used first line with diet"

The complainant said that how these words were interpreted was a matter of considerable concern. When he showed the advertisement in question "cold" to doctors they believed that ispaghula lowered cholesterol by 10%.

The only value of an agent (statin, fibrate, ispaghula etc) with diet was that it should have an effect over and above diet. This was clearly not 10%. For total cholesterol at 12

weeks on "intention to treat" the falls were 2.7% and 3.1% for 7g and 10.5 g/day ispaghula.

These were the only relevant values for this study and their value and interpretation could be questioned.

"As a manuscript submitted to a major journal for publication it surprised the complainant that it included no statistical analysis at all and no p values. It was stated that falls on treatment were significantly greater but no statistical evidence was provided"

The complainant said that the BMJ's rejection of the first manuscript was inevitable. The complainant was also highly critical of the second manuscript and set out a detailed critique of it.

The complainant commented that not having patent protection was no excuse for hiding inadequate data on which sales were to be based.

"Advertising should say that a cholesterol fall of a certain percentage was seen after diet, rather than with diet. It was important that the agent used to lower cholesterol has an effect additional to the dietary input"

The product licence for all lipid lowerers required that dietary modification (and lifestyle) should be used together to obtain optimum effect. Ispaghula was no different to any other agent.

All other agents made claims of what their agent would do against placebo. This should best be after diet of course, but not with diet.

The complainant noted that Reckitt & Colman here accepted that its product did not reduce cholesterol by 10%. The company said that "Reckitt & Colman of course agreed that a cholesterol lowering agent should have an effect additional to the dietary input and it had shown beyond reasonable doubt that this was the case with Fybozest."

The complainant contended that if Reckitt & Colman's data were those provided then it had not so shown. The company's 10% claim was now one of 2.7% or 3.1% and no p value on an "intention to treat" basis was given.

"I had believed that if data was to be used in advertising it had to be in the public domain, or at least as a minimum, within limited circulation to those who enquired about it. It seemed unacceptable that claims could be made in advertising when the data was not available to individuals being targeted by that advertising"

The complainant said that when he had obtained the draft of Reckitt & Colman's "on file data" it was via the Authority, it being said that confidential data was not normally released. The complainant's first letter in November was a one line request for "data on file".

The complainant said that this was exactly the reply given to him on the telephone when he was put through to what had assumed, and still believed was the medical department. He had kept no log, but it was clear that neither did Reckitt & Colman, however efficient its internal system.

The complainant said that it was not acceptable to be unable to be shown data on which doctors were supposed to act in patients' interest and doubted if it would be the BMJ's intent for its editorial policy to dictate patient care in this way.

It was to an extent the very extensive dissemination of inadequate advertising on a new product that was so concerning.

The complainant considered that an advertisement which said "Fybozest might lower cholesterol by 3%" would be acceptable (although no p value for the 12 week intention to treat comparison was given). One had to remember that the coefficient of variation of cholesterol in an individual (independent of any other alteration, diet, bias etc) was +/- 6%. This meant that the mean +/- 2 SD was +/- 12%. For a cholesterol of 5mmol, a value could be between 4.4 and 5.6mmol by chance. Measuring two baseline values made this less at perhaps +/- 5% (ie 5mmol/litre (4.75 to 5.25)).

APPEAL BOARD RULING

The Appeal Board noted that, according to the prescribing information in the advertisement, Fybozest was to be used in conjunction with dietary modification.

The Appeal Board considered that the claim in question "Fybozest .... It quite simply lowers cholesterol, by up to 10% when used first line with diet" was ambiguous. It could be taken to mean that Fybozest, ie "It", lowered cholesterol by up to 10% and not that it was the combination of Fybozest plus diet. This impression was reinforced by the advertisement's major headline "Announcing Fybozest for mild to moderate primary hypercholesterolaemia. It simply lowers cholesterol". The Appeal Board noted that dietary modification alone would have a significant effect on cholesterol and it was not clear what proportion of the claimed 10% was due to the diet alone and what additional effect Fybozest had.

The Appeal Board identified flaws and inconsistencies in the presentation, analysis and conclusions drawn from the data provided. Versions of the data presented in the product monograph, the short paper and the more detailed paper differed from one another in certain respects. The claimed 10% lowering of cholesterol had been derived from the phase of the study (weeks 13 to 24) which was not placebo controlled and so the fall could have been due to dietary manipulation alone.

The Appeal Board considered that the claim was misleading and had not been substantiated. The Appeal Board ruled breaches of Clauses 7.2 and 7.3 of the Code.

The appeal in this case was successful.

During its consideration of this case the Appeal Board expressed its concern regarding the way in which Reckitt & Colman had dealt with requests for information from the complainant. The Appeal Board considered, however, that Reckitt & Colman had not provided the data because it genuinely thought that once a case was before the Authority then all information should be passed through the Authority and not direct to the complainant. The Appeal Board asked that companies be reminded of their obligations under Clause 7.4 of the Code to provide substantiation without delay following a request from a health professional.

Complaint received **21 November 1996**

Case completed **2 April 1997**

CASE AUTH/478/11/96

ANON v PFIZER

Hospitality for a consultant

An anonymous complaint was received about a meeting held by Pfizer with a doctor from a hospital in relation to problems with a clinical trial. The meeting consisted of a visit to the opera followed by dinner. There were six attendees, the doctor and his wife, the company medical adviser, a clinical research project manager and the medical representative for the hospital and his wife.

The Panel ruled that the meeting came within the scope of the Code. The clause relating to meetings, Clause 19, made it clear that the Code applied to all meetings with members of health professions regardless of whether any meeting itself was promotional or not. The Panel ruled that the hospitality was unacceptable given the events and the inclusion of the doctor's wife. This was accepted by Pfizer. The Panel ruled a breach of Clause 2 as the events brought discredit upon and reduced confidence in the pharmaceutical industry. The Panel also decided to report Pfizer to the Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure. Pfizer appealed the ruling of a breach of Clause 2.

The Appeal Board noted that the meeting was a discussion with a clinical trialist. It was a non-promotional meeting. Given the nature of the meeting and the facts of this particular case, the Appeal Board considered that it did not warrant a ruling of a breach of Clause 2 of the Code. The appeal was successful. Given the ruling of no breach of Clause 2, the Appeal Board decided that there was no need to take any further action regarding the report from the Panel.

COMPLAINT

An anonymous complaint was received which was on hospital notepaper. The complainant said that he/she held a senior medical position at the hospital.

The complainant stated that a senior doctor from the hospital and his wife were taken to the opera by a representative of Pfizer Limited. The complainant understood that the Code of Practice prohibited such blatant entertaining without an educational content. The complainant said that this set a bad example and put into question the medical impartiality of the doctor with reference to Pfizer products promoted within the hospital.

In writing to the company, the Authority drew attention to the provisions of Clauses 2, 15.2 and 19 of the Code.

RESPONSE

Pfizer objected most strongly to the manner in which the allegation had been made. As a matter of principle, it objected to responding to an unsigned complaint which was defamatory both of Pfizer and the doctor concerned. The company doubted its authenticity; among other reasons, it seemed unlikely that a senior medical person at the hospital would misspell the name of the doctor.

The events related to dealings between Pfizer's medical adviser and the doctor regarding a clinical trial of one of Pfizer's products. As such they were totally unconnected with promotion and, in the company's view, the Code had no application to them.

Prior to the relevant day, the medical adviser was in touch with the doctor in connection with a clinical trial. There were certain problems which had arisen with the administration of the trial in its early stages and there was a need for an investigator's meeting to resolve the problems. The doctor wrote to the medical adviser indicating several concerns about the administration and suggesting that it would be a good idea to have a meeting in London one evening with the medical adviser, a clinical research project manager employed by a non-Pfizer company, and others involved in the study so that any further problems could be anticipated.

It had not been easy to find a convenient date but ultimately 7 November was agreed. The medical adviser had been told by the doctor of his interest in opera and had invited him to attend an opera and have the business meeting afterwards. The meeting was expected to be difficult from a business aspect in view of the expressed concerns about the administration of the study. The medical adviser wished to precede the meeting with a pleasant social occasion.

One of Pfizer's hospital representatives was told of the meeting in the course of a conversation with the doctor concerned whom he met frequently. The representative's wife was able to obtain opera tickets through her business contacts. As a result the representative and his wife were invited by the medical adviser to join the group for the evening. The tickets for the opera cost £45 each and the event was a gala evening for the Red Cross.

The party who attended the opera were the medical adviser, the clinical research project manager, the doctor and his wife and the representative and his wife. Pfizer understood that the doctor's wife was paid by him as an administrative assistant. Following the opera, all six people had dinner at a restaurant at a total cost of £158. The business discussions took place over and after the meal and finished around 12:45 am, about two hours after the opera finished. No transport was provided by Pfizer. Drinks during the interval cost £31.40.

The representative was prepared to attend the event in question because his wife had been involved in acquiring the tickets and the event had absolutely no promotional content or intent. The representative had no business discussions with the doctor at any time during the evening and their only exchanges were of a social nature.

PANEL RULING

The Panel noted Pfizer's comments about the anonymous complaint. It was unfortunate that the complaint was not signed, though perhaps understandable. It was a well established principle that anonymous complaints were considered under the Code.

The Panel first had to decide whether or not the meeting came within the scope of the Code. Clause 1.2 defined promotion as including the sponsorship of scientific meetings including the payment of travelling and accommodation expenses in connection therewith. This was included in the Code as a result of the EC Council Directive on the advertising of medicinal products for human use. Clause 19.1 of the Code stated that companies were permitted to provide appropriate hospitality to members of the health professions and appropriate administrative staff in association with scientific and promotional meetings, scientific congresses and other such meetings. The supplementary information to Clause 19.1 gave examples of meetings such as small lunchtime audio-visual presentations in a group practice, hospital meetings and meetings at postgraduate education centres, launch meetings for new products, management training courses, meetings of clinical trialists, patient support group meetings and satellite symposia through to large international meetings organised by independent bodies with sponsorship from pharmaceutical companies.

The Panel considered that the Code applied to all meetings which, according to the definition in Clause 1.2, would thus be defined as promotion. The content of any particular meeting could be either promotional or non promotional but it would still come under the definition of promotion as set out in Clause 1.2 and be subject to the Code. The meeting organised by Pfizer for a clinical trialist was therefore subject to the Code.

The Panel had a number of concerns about the evening. The Panel noted that the meeting in question started after the opera and finished two hours later at 12:45 am. The Panel considered that the evening's events were not appropriate in relation to the requirements of Clause 19.1. The visit to the opera, not the discussion about the trial, appeared to be the dominant purpose of the evening. This was not in accordance with Clause 19 which stated that any hospitality must be secondary to the purpose of the meeting. Further, the supplementary information to Clause 19 stated that meetings that were wholly or mainly of a social or sporting nature were unacceptable.

The involvement of the doctor's wife was unacceptable in that the Code stated that hospitality must not extend beyond members of the health professions or appropriate administrative staff. The supplementary information stated that hospitality must not extend to spouses and others unless that person qualified as a proper delegate or participant at the meeting in their own right. The Panel did not accept that the doctor's wife was an appropriate administrative member of staff as provided for by the Code.

The Panel considered that overall the events were unacceptable and therefore ruled a breach of Clause 19 of the Code. The Panel considered that the events brought discredit upon and reduced confidence in the pharmaceutical industry and therefore ruled a breach of Clause 2 of the Code.

The Panel also decided to report Pfizer to the Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

APPEAL BY PFIZER

Pfizer said that the events on 7 November 1996 took place in the belief that the Code did not apply because they were totally unconnected with promotion. Having reviewed the Panel's ruling, Pfizer accepted the finding that the Code did apply to the meeting, although this was not without challenge. As a consequence the company accepted the finding that the hospitality provided was at a level beyond that permitted by Clause 19 of the Code. The company did not provide hospitality at non-promotional meetings attended by members of the health professions at a level beyond that permitted by Clause 19.

Pfizer did not accept that the circumstances warranted a finding of a breach of Clause 2. The Panel's findings appeared to be based on its view that the visit to the opera was the dominant purpose of the evening and that the meeting was wholly or mainly of a social nature. More details about the background and the particular problems with the study were provided.

A copy of a letter dated 19 September 1996 from the doctor, indicating his displeasure with Pfizer, his concerns about the administration of the clinical trial and suggesting a meeting in London "one evening" was provided. A letter from the clinical research project manager to the medical director dated 10 January about the meeting was also provided.

Pfizer said that there were significant business matters to be discussed. The events of the evening of 7 November were arranged with the object of settling those business matters and that they did in fact do so. The doctor's unit was an important investigational centre for Pfizer.

Pfizer said that the attendance at the opera was a subsidiary matter but important to Pfizer because there had been ill-feeling from the doctor and there was a wish by Pfizer's medical adviser to overcome that prejudice by preceding the business discussions with a pleasant social event.

The finding was out of proportion to the circumstances as Clause 2 was reserved for matters of particular excess. The meeting was a genuine business meeting lasting over a period of about two hours, albeit at a relatively late hour. The doctor himself suggested an evening meeting. The breach of Clause 19 was not excessive to an extent justifying particular censure. The cost of the dinner was, especially by London standards, reasonable at £26 per head and the total cost of the evening per person was £76.50. The opera was a gala event for the Red Cross, a health-related charity. To support such an event, with the doctor and his wife as the company's guests, should not bring discredit upon the industry. Although the medical adviser was familiar with the Code he genuinely believed that the business meeting with the doctor was not subject to the Code. The event was isolated as Pfizer did not make a practice of providing hospitality at meetings attended by members of the health professions at a level beyond that permitted by Clause 19.

Pfizer submitted that if a breach of Clause 2 were found on this occasion it would be difficult to see circumstances in which a breach of Clause 19 would not automatically involve a breach of Clause 2. The supplementary information, in its reference to reserving Clause 2 to a sign of particular censure, was designed to avoid this consequence.

APPEAL BOARD RULING

The Appeal Board noted that this was the first case it had considered about a clinical trial meeting since the Code had been changed to take into account the EC Directive on the advertising of medicinal products for human use and The Medicines (Advertising) Regulations 1994.

The Appeal Board considered that the meeting was non-promotional, being a discussion with a clinical trialist about problems with a particular trial. It was seen differently to a promotional meeting. The Appeal Board considered that the meeting was a genuine meeting to sort out difficulties between the company and the clinical trialist. It was non-promotional. Pfizer had accepted that the events were in breach of Clause 19 of the Code. The Appeal Board considered that, given the nature of the meeting, and the facts of this particular case, it did not warrant a ruling of a breach of Clause 2 of the Code which was reserved as a sign of particular censure. The Appeal Board therefore overturned the Panel's ruling and ruled no breach of Clause 2. The appeal was therefore successful.

Given the ruling of no breach of Clause 2, the Appeal Board decided that there was no need to take any further action regarding the report from the Panel made in accordance with Paragraph 8.2 of the Constitution and Procedure.

Complaint received **22 November 1996**

Case completed **22 January 1997**

CASE AUTH/479/12/96

SMITHKLINE BEECHAM v BAYER

Promotion of Ciproxin

SmithKline Beecham complained about the promotion of Ciproxin by Bayer. There were four items at issue and a number of allegations were made.

Firstly, with regard to a sensitivity chart, the Panel considered that given the data, the figure given in the chart for the MIC value of co-amoxiclav versus *E coli* was misleading in breach of the Code. The Panel ruled that the shading used in the chart was inaccurate as there had been an error. The Panel ruled that there was no breach of the Code with regard to an allegation that it was inappropriate to use data on file as a reference.

Secondly, with regard to a "Dear Doctor" letter, the Appeal Board upheld the Panel's ruling of a breach, following an appeal from Bayer, that a claim referring to plasmid resistance to both the amoxycillin and the clavulanic acid components of co-amoxiclav had not been substantiated. There was no evidence at the present time regarding the clinical relevance of plasmid mediated resistance to clavulanic acid. No breach was ruled regarding a claim highlighting the difference in eradication rates for Ciproxin and co-amoxiclav. The claim did refer to the similar clinical results. The Panel ruled no breach in relation to a claim that Ciproxin demonstrated fewer gastrointestinal side effects than co-amoxiclav. A claim referring to the risk of pseudomembranous colitis was ruled in breach by the Panel as it was not capable of substantiation. The Appeal Board overturned the Panel's ruling and ruled no breach of the Code following an appeal by Bayer when additional data was provided. The Panel ruled that the letterhead was misleading as it referred to intravenous Ciproxin whereas the text referred to oral therapy.

Thirdly, with regard to a leavepiece, the Panel's rulings of no breach regarding the comparison of eradication rates and the comparison of gastrointestinal side effects also applied to the leavepiece. The Appeal Board's ruling of a breach concerning plasmid mediated resistance also applied to the leavepiece. The Panel ruled that a claim that Ciproxin was more convenient than co-amoxiclav was not unreasonable given the dosing schedule and packaging.

Finally, with regard to a journal advertisement, the Panel ruled no breach of the Code with regard to the use of data from blood culture isolates. It had been made clear to readers that blood culture isolates had been used for the sensitivity tests. The Panel did not consider that a section referring to *S pneumoniae* was unreasonable. It did not refer to co-amoxiclav. The section referred to penicillin and erythromycin. No breach of the Code was ruled.

SmithKline Beecham Pharmaceuticals UK complained about the promotion of Ciproxin by Bayer plc Pharmaceutical Division. There were a number of items at issue. The allegations were considered as follows:

A SENSITIVITY CHART

The sensitivity chart was headed "Comparative *in vitro* antibacterial spectra and MIC90s". It compared Ciproxin with a number of antibiotics, including SmithKline Beecham's product co-amoxiclav (Augmentin), with respect to their effect on various named organisms. There were three allegations.

1 MIC value of 64 for co-amoxiclav versus E coli

COMPLAINT

SmithKline Beecham said that the efficacy of Augmentin against *E coli* both clinically and *in vitro* was well documented in the literature: Barrett (1996), Thomson (1992), Kucers & Bennett (1988), Slocombe (1987), Gallacher *et al* (1996), Flavell-Matts SG *et al* (1985), Nishiura T (1982). Therefore, the data quoted was unbalanced. The company was unable to trace a reference quoting an MIC of 64 for Augmentin to *E coli* as given in the chart. Kucers and Bennett (1988) quoted an MIC of 8 which was designated sensitive. A breach of Clause 7.2 was alleged.

RESPONSE

Bayer submitted that the figure, 64, was quoted in good faith. It was apparent that there was a very variably quoted MIC90 for co-amoxiclav vs *E coli* in the literature.

In a personal communication dated 5 December 1996, Felmingham, the source of the data, had indicated that on reflection, the population of original isolates tested to produce a MIC90 of 64 ug/ml contained 25% of strains resistant to ureidopenicillins, and that the isolates were possibly 'epidemiologically unrepresentative'. The author now indicated that there were methodological difficulties as well as various methods of testing the comparators, especially with regard to the clavulanic acid component.

SmithKline Beecham had referred to number of references. Barrett (1996) was purported to have submitted a paper to the JAC, but the editorial assistant had no knowledge of such a submission - even if it had been rejected, it was not in the public domain at this juncture. The British Library advised Bayer that "Postgrad", where the Slocombe reference was published, was not a journal that it was aware of.

The calculated, not stated, MIC90 from the Thomson (1992) paper was 16 ug/ml. Flavell-Matts did not quote any MICs. The Gallacher data was based on only 16 isolates of *E coli* from patients on failed therapy - the mean MIC90 was 8 ug/ml pre-treatment, 16 ug/ml post treatment.

Importantly, Felmingham (1994), quoted a MIC90 of> 128ug/ml for co-amoxiclav against *E coli*, with a range of 2 - > 128 ug/ml. Rubio, (1989), indicated that the MIC90 for ampicillin-resistant *E coli* varied over 12 years from 16 - 64 ug/ml in the range of 2 - 128 ug/ml.

In refuting a breach of Clause 7.2, Bayer was willing, after open discussion with SmithKline Beecham, to amend the figure of 64 if appropriate.

PANEL RULING

The Panel noted that SmithKline Beecham had referred to a number of studies in its complaint. None had been

provided. It further noted that Bayer had said that there was a very variably quoted MIC90 for co-amoxiclav vs *E coli* in the literature and the view of the the source of the figure of 64 that it might be based on isolates that were possibly epidemiologically unrepresentative.

The Panel considered that the position as to the true figure for co-amoxiclav was not as clear cut as implied by the chart. Given the data, the figure of 64 given in the chart was misleading and a breach of Clause 7.2 of the Code was ruled.

2 Error in shading

Two colours were used in the chart, light blue to indicate ≤ 90% of strains were sensitive and dark blue to indicate > 90% of strains were sensitive.

COMPLAINT

SmithKline Beecham alleged that there was an inconsistency in certification of sensitive/non sensitive organisms. For example, *Klebsiella spp* was deemed insensitive to co-amoxiclav (as the relevant box was shaded light blue) and yet *B fragilis* was sensitive to ciprofloxacin (as the relevant box was shaded dark blue.) However, both MIC values were equivalent to the breakpoint of the antibiotic. A breach of Clause 7.2 was alleged.

RESPONSE

Bayer accepted that an unfortunate typographical error resulted in the colouring of the box relating to Ciproxin and *B fragilis* being transposed with that of the adjacent *Fusobacterium spp* box. The item had already been withdrawn and would be corrected.

PANEL RULING

The Panel noted that there had been an error in the shading of the boxes as alleged. This was inacurate and the Panel therefore ruled a breach of Clause 7.2 of the Code.

3 Use of data on file reference

COMPLAINT

SmithKline Beecham alleged that as MIC values for Augmentin against bacteria were well documented in the literature, it seemed inappropriate to use Bayer data on file. A breach of Clause 7.5 was alleged.

RESPONSE

Bayer submitted that by using data on file rather than six different sources of data, it had striven to provide consensus data.

Different sources of data were likely to produce different MIC90 data, as outlined in Point 1 above. Whilst it would be even more accurate to quote ranges of MIC90 data (eg 2 - > 128 ug/ml), it would make it impossible to colour-code such information regarding probable sensitivity or otherwise and this would be to the physician's potential disadvantage.

PANEL RULING

The Panel noted that Clause 7.5 of the Code required that a reference be given when referring to published studies. There was no requirement to reference any other material. All material must be capable of substantiation and such substantiation provided on request.

There was no specific prohibition on using data on file as a reference. The chart was not one that needed to be referenced as no mention was made of published studies. The Panel therefore ruled no breach of Clause 7.5 of the Code.

B "DEAR DOCTOR" LETTER

The "Dear Doctor" letter was sent to hospital doctors (microbiologists, general medicine, geriatricians, orthopaedic surgeons, general surgeons). The letter was printed on paper headed "IV Ciproxin 400mg Rapid and Reliable Recovery". The heading to the letter itself was "Ciproxin in comparison to co-amoxiclav".

4 Claim "There is now evidence which reports on emerging plasmid-mediated resistance to both the amoxycillin and the clavulanic acid components of co-amoxiclav"

The claim was referenced to a letter in The Lancet from Thompson (1994).

COMPLAINT

SmithKline Beecham alleged that the claim was invalid and not substantiated by the reference quoted. The reference described a rise in TEM-1 b-lactamase capable of hydrolysing the later generation cephalosporins. It did not refer to clavulanic acid or non b-lactamase mediated resistance to clavulanic acid and therefore co-amoxiclav. There had been no increase in the incidence of resistance to Augmentin over the last 14 years (Neu et al, 1993). Breaches of Clause 7.2 and 7.3 were alleged.

RESPONSE

Bayer submitted that SmithKline Beecham might have missed the clear reference to clavulanic acid in the Thomson paper which stated.

> "... TEM-1 b-lactamase can adapt to become resistant to b-lactamase inhibitors".
>
> "TEM resistant to clavulanic acid (TRC-1), a novel TEM-derived b-lactam with increased resistance to b-lactamase inhibitors, was detected in urinary *E coli* in Edinburgh in 1990".

SmithKline Beecham claimed there had been no increase in the incidence of resistance to Augmentin over the last 14 years, but Professor Speller had shown otherwise in relation to *H influenzae*.

PANEL RULING

The Panel noted that the only data supplied to support the claim was a letter by Thomson dated 1994. The personal communication from Speller had not been provided by Bayer.

The Panel considered that the claim had not been substantiated to its satisfaction. The evidence provided, although it did refer to clavulanic acid, was very limited. The Panel therefore ruled a breach of Clause 7.3 of the Code.

APPEAL BY BAYER

Bayer explained that antibiotic resistance could result from several different mechanisms. Details were provided.

The existence of the TEM-1 plasmid which resulted in the production of b-lactamase thus conferring resistance to the amoxycillin component, was very widely reported. The TEM-1 derived plasmid which resulted in clavulanic acid resistance was increasingly reported and was not a single report confined to Thomson's letter to The Lancet.

A report from Professor Peter Hawkey, a recognised expert in the field of antimicrobial resistance mechanisms, noted:

> "It is my opinion that the complaint was not valid, as careful reading of the cited letter by Thomson *et al* does support the original claim. In addition an overwhelming body of independent scientific evidence supports the statement"

Bayer submitted that over the last five years there had been numerous reports, in peer reviewed journals of novel plasmids identified in clinical isolates that conferred resistance to the clavulanic acid component of co-amoxiclav. A number of studies were cited to provide considerable further substantiation of the claim. Details were provided as follows:

Thomson (1992) that

> "... a novel TEM enzyme, identified in a clinical *E coli* strain isolate in Scotland, which confers resistance to the combination of amoxycillin/clavulanic acid".

Thomson went on to comment

> "... the novel enzyme was approximately 100-fold less sensitive to the action of this inhibitor".

Vedel (1992) reported discovery of b-lactamases that were poorly inhibited by clavulanic acid, explaining that

"The novel plasmid encoded enzyme produced by the two isolates of *E coli* appeared to be almost identical and to be derived from TEM enzymes".

Sirot (1994) investigated twenty clinical isolates of *E coli* resistant to amoxycillin. He stated

> "Combining amoxycillin with b-lactamase inhibitors ..... had only modest potentiating effects on the activities of this agent .....".

MIC values in the presence of clavulanic acid in the Sirot work ranged from 256->2048mg/L.

The high level of resistance reported by Sirot, was confirmed by Henquell (1994) to be due to b-lactamases which were TEM-1 derived, ie plasmid mediated resistance to clavulanic acid. 40% of the strains of *E coli* studied were intermediate or resistant to co-amoxiclav. Henquell also commented

> "The total prevalence of IRT producing strains was 4.9%. The emergence of this novel resistance mechanism could be related to the frequent use of clavulanate-containing formulations in hospitals and in general practice".

Blazquez (1993) documented a further new clinical strain of *E coli* with transferable plasmid-mediated resistance to clavulanic acid. Importantly he commented

> "The potential spread of these IRT b-lactamases among *E coli* populations is worrisome. The location of the resistance determinant in a conjugative plasmid and its presumptive transposable nature may favour its dissemination among other micro-organisms. The widespread use of b-lactamase inhibitors in clinical practice may create the necessary selective force to produce such undesired effects".

Bayer provided the Speller reference in which the sensitivities to *H influenzae* from cultured blood isolates with co-amoxiclav changed from 98.9% susceptible in 1989 to 94.9% in 1994. Professor Speller commented that

> "Other therapeutic options such as co-amoxiclav also experienced increasing bacterial resistance".

The company accepted that there was no evidence at the moment regarding the clinical relevance of plasmid mediated resistance. The studies referred to by Bayer had not been carried out on patients. The company had not made any clinical claims in this regard.

APPEAL BOARD RULING

The Appeal Board noted that the studies presented by Bayer had been carried out on *E coli* which was rarely implicated in respiratory infections although antibiotic resistant *E coli* was of relevance in discussion of mechanisms of resistance. The Appeal Board accepted that the company had some evidence regarding plasmid resistance to clavulanic acid in the studies submitted. The letter in question, however, referred to the clinical use of Ciproxin and co-amoxiclav. It was advocating prescribing Ciproxin instead of co-amoxiclav and implied that plasma mediated resistance was a clinical issue. The evidence supplied by Bayer was not sufficient to substantiate the claim in question given its context as there was no evidence at the moment regarding the clinical relevance of plasmid mediated resistance to clavulanic acid.

The Appeal Board agreed with the Panel that the claim had not been substantiated and upheld the Panel's ruling of a breach of Clause 7.3 of the Code.

The appeal on this point therefore failed.

5 Claim "...Ciproxin 500mg bd yields a superior bacteriological eradication rate to co-amoxiclav 625mg tds (100% vs 87.5% $p \leq 0.009$) whilst showing similar clinical results"

COMPLAINT

SmithKline Beecham alleged that it was misleading in this instance to quote bacterial eradication rates. The reference for the claim, Barash 1991, showed that clinical success was equivalent, although clinical cure was higher for co-amoxiclav than for ciprofloxacin. A breach of Clause 7.2 was alleged.

RESPONSE

Bayer said that the efficacy of antibiotic drugs had been defined in three ways by Davis (1996):-

Clinical cure	:	resolution of all signs and symptoms of infection without recurrence
Clinical improvement	:	signs and symptoms show improvement from baseline
Bacterial eradication	:	complete eradication of the pathogen without recurrence, reinfection or super infection

It was totally appropriate to use bacteriological eradication rates to highlight different outcomes between antibiotic therapies. It was agreed that the Barash paper showed a 96% clinical success rate for co-amoxiclav and 94% for ciprofloxacin (non significant.) The phrase "similar clinical results" was used to highlight this lack of statistical significance.

PANEL RULING

The Panel noted that the claim referred to the similar clinical results of co-amoxiclav and Ciproxin in addition to highlighting the difference in eradication rates. Given the context, the claim was not unreasonable and the Panel therefore ruled no breach of Clause 7.2 of the Code.

6 Claim "Not only does Ciproxin demonstrate significantly fewer gastro-intestinal side effects than co-amoxiclav (p ≤0.004),..."

COMPLAINT

SmithKline Beecham alleged that the reference quoted was unavailable from the British Library. The incidence of adverse events found with ciprofloxacin (Ciprofloxacin Monograph 1992) was similar to that found with Augmentin (Neu *et al*, 1993.) A breach of Clause 7.2 was alleged.

RESPONSE

Bayer said that it preferred to use comparative data where it existed though relatively few double-blind studies had been undertaken using these comparator agents.

Bayer said that SmithKline Beecham had been supplied with a copy of the Barash paper (the reference to the claim) on 6 November 1996 in response to a request received on 25 October. The Barash paper showed that of 153 valid patients, gastrointestinal side effects occurred in 18 (18%) and 35 (36%) patients respectively for ciprofloxacin and co-amoxiclav (p ≤0.004)

In another, double blind, prospective study, Legent (1994) reported total side effects in 31/124 (25%) patients treated with co-amoxiclav and in 15/121 (12.4%) of those treated with ciprofloxacin (p=0.012.) The number of gastrointestinal adverse effects was 35 (co-amoxiclav) and 9 (ciprofloxacin.) The authors stated that

> "Clinical tolerance was significantly better with ciprofloxacin, essentially due to a large number of gastro-intestinal related side-effects in the amoxycillin/clavulanic acid group".

SmithKline Beecham suggested that the Ciprofloxacin Monograph 1992 and the Neu paper showed a similar incidence of gastrointestinal side effects. The respective figures were 4.9% of patients treated with ciprofloxacin and 8.4% of patients treated with co-amoxiclav. Both these references were reviews of other works and therefore did not allow direct comparisons between the two agents in the same patient population.

PANEL RULING

The Panel noted that SmithKline Beecham had been provided with the Barash study by Bayer. It was not relevant whether or not a reference was available from the British Library.

The Panel examined the data and noted that the Barash study had evaluated 196 patients in the safety analysis. The study said that the incidence of adverse events was comparable for the two treatment groups with the exception of the digestive system. The overall incidence of adverse events was significantly greater for the amoxicillin/clavulanate patients than for the ciprofloxacin patients. The Panel considered that the claim was acceptable and therefore ruled no breach of the Code.

7 Claim "... but the risk of pseudomembranous colitis is minimised with Ciproxin - less than 0.01% in a worldwide study of 9,466 patients"

This claim together with the claim in point 6 above appeared as one sentence in the letter.

COMPLAINT

SmithKline Beecham alleged that the claim was not substantiated by the reference given (Schacht *et al* 1989). SmithKline Beecham said that there was no comparison to Augmentin in the reference and yet this claim implied that there was. The company had done an extensive literature search which had failed to find a direct comparison of figures indicating the incidence of PMC with Augmentin. It was expected that the incidence of PMC with Augmentin was comparable to that with ciprofloxacin.

A breach of Clause 7.3 was alleged.

RESPONSE

Bayer submitted that the claim referred only to Ciproxin and not to co-amoxiclav. In the complete sentence the reference number following the "p" value (Barash) clearly separated two unrelated clauses. The Barash paper did not mention pseudomembranous colitis (PMC).

Bayer pointed out that co-amoxiclav and its constituents had been implicated as a potential cause of PMC elsewhere. Buckley (1996) classified co-amoxiclav in the group of antibiotics which frequently caused *Clostridium difficile* induced colitis (CDIC) and Kelly (1994) listed amoxycillin as a frequent inducer of CDIC.

PANEL RULING

The Panel considered that the sentence could have been better written to ensure that readers were clear that no comparison was intended between the risk of pseudomembranous colitis with Ciproxin and the risk with co-amoxiclav. The Panel considered that the letter was ambiguous in this regard, particularly, as it was headed "Ciproxin in comparison to co-amoxiclav". In the Panel's view readers would assume that the claim was comparative and this could not be substantiated as there was no comparative data. A breach of Clause 7.3 was ruled.

APPEAL BY BAYER

Bayer accepted the Panel's view that the letter was ambiguous and that readers might have understood that a direct comparison was being made between co-amoxiclav and Ciproxin with respect to the likelihood of pseudomembranous colitis. However, this comparison could be substantiated from several sources.

Pseudomembranous colitis could result from antibiotic therapy. Some antibiotics had a significant effect on the normal colonic flora, which could result in the proliferation of *Clostridium difficile*. Kelly (1994) reported that

> "*C difficile* infection is responsible for virtually all cases of pseudomembranous colitis".

The Merck Manual (1992) cited penicillins (and hence co-amoxiclav) as one of the groups of antibiotics most frequently implicated in pseudomembranous colitis. There were numerous publications that classified antibiotics by their propensity to cause *Clostridium difficile* induced colitis (CDIC). Penicillins (co-amoxiclav) were consistently cited as causing CDIC more frequently than quinolones (Ciproxin).

Buckley (1996) classified co-amoxiclav in the group of antibiotics which frequently caused CDIC, whilst quinolones were in the group which rarely caused CDIC. Reinke (1994) concurred with this. Kelly listed amoxycillin (and hence potentiated amoxycillin) as a frequent inducer of CDIC.

Bartlett (1990) analysed the antimicrobials received by 329 patients with antibiotic induced diarrhoea who tested positive for *C difficile* toxin. Of those patients who had single antibiotic treatment during the six weeks before symptoms appeared 82 received ampicillin or amoxycillin.

Vautrin (1993) reported that out of 16 geriatric patients colonised with toxigenic *C difficile* in 15 cases antibiotic preceded the resultant diarrhoea. He stated

> "Amoxycillin + clavulanic acid treatment was the most frequently responsible (65%)"

Reinke discussed the properties of antibiotics associated with a high risk of CDIC

> "Antimicrobials that have the most deleterious effect on resistance to colonization are also among those most commonly associated with CDIC. Conversely antimicrobials antimiobials known to spare the normal colonic microflora, especially the obligate anaerobes, appear much less likely to precipitate CDIC. The latter include the fluoroquinolones, which have relatively poor antianaerobic cover".

Bayer submitted that co-amoxiclav had an antimicrobial effect on anaerobic organisms. SmithKline Beecham had specifically promoted the broad spectrum of activity of co-amoxiclav highlighting its anaerobic cover and consequent usefulness in surgery. Reinke's statement above explained why clavulanate potentiated amoxycillin (co-amoxiclav) was classified by Reinke and others (Buckley, Kelly) as an agent which "frequently" causes CDIC, whilst Ciproxin "rarely" caused CDIC.

Reference was made to an abstract to be presented at the 20th International Congress of Chemotherapy in Australia in June/July 1997. The abstract referred to a retrospective study on 430 patients, the results of which suggested that co-amoxiclav was a significant risk factor associated with *C difficile* infections. Ciprofloxacin was not found to be a risk factor.

APPEAL BOARD RULING

The Appeal Board noted that the ruling had to be made on the material available at the time the "Dear Doctor" letter was used.

The Appeal Board accepted that there was data to show that co-amoxiclav was more likely to be associated with the risk of pseudomembranous colitis than Ciproxin. The Appeal Board considered that the data substantiated the claim "but the risk of pseudomembranous colitis is minimised with Ciproxin ..." and no breach of the Code was ruled.

The appeal on this point was therefore successful.

8 Letterhead "IV Ciproxin 400mg"

COMPLAINT

SmithKline Beecham pointed out that the letter appeared on paper headed "IV Ciproxin 400mg" whereas the references used to support the letter referred largely to oral and not IV ciprofloxacin. The references used were therefore inappropriate for IV ciprofloxacin and did not support the claims made in the text. A breach of Clause 7.2 was alleged.

RESPONSE

Bayer accepted that there was an unfortunate error in terms of the letterhead in relation to the contents and references. The letterhead was inappropriate as the text related to oral therapy.

PANEL RULING

The Panel noted that the letterhead referred to IV Ciproxin whereas the material to support the letter largely referred to oral Ciproxin. The letterhead was therefore misleading and the Panel ruled a breach of Clause 7.2 of the Code.

C LEAVEPIECE "GO TO WORK ON INFECTION"

The leavepiece (ref 9BCPT745) was used by general

practitioner representatives but was not part of the current promotional campaign. There were four allegations.

9 Comparison of bacteriological eradication rates

This section was headed "Working in comparison with co-amoxiclav" and was followed by the statement. "Although clinical success rates were not significantly different, bacteriological eradication rates were as follows". This was followed by an illustration of a road sign showing a fork in the road with the "straight on" arrow labelled as "Ciproxin 100%" and the right hand fork arrow labelled as "co-amoxiclav 87.5%" A p value, p $\leq$0.05, was also given.

COMPLAINT

SmithKline Beecham alleged that it was misleading to quote bacterial eradication rates. Clinical success was equivalent for co-amoxiclav and ciprofloxacin. A breach of Clause 7.2 was alleged.

RESPONSE

Bayer's response was similar to that given in point 5 above.

PANEL RULING

The Panel noted that this was similar to point 5 above, although the layout and emphasis were different. The text did state that clinical success rates were not significantly different although more prominence, by virtue of an illustration, was given to the differences in bacteriological eradication rates. On balance the Panel decided that the layout was not unacceptable and no breach of the Code was ruled.

10 Claim "There is now evidence of emerging plasmid-mediated resistance to both the amoxycillin and the clavulanic acid elements of co-amoxiclav"

COMPLAINT

SmithKline Beecham's allegation was similar to that in point 4 above. Breaches of Clauses 7.2 and 7.3 were alleged.

RESPONSE

Bayer's response was similar to that given in point 4 above.

PANEL RULING

The Panel noted that this was similar to point 4 above and its ruling of a breach of Clause 7.3 would also apply to point 10.

APPEAL BY BAYER

Bayer's appeal was similar to that given in point 4 above.

APPEAL BOARD RULING

The Appeal Board noted that this allegation was similar to point 4 above. The claim appeared in a slightly different context to that in point 4 but nevertheless the Appeal Board considered that its ruling in point 4 would also apply here. The Appeal Board therefore upheld the Panel's ruling of a breach of Clause 7.3 of the Code.

The appeal on this point therefore failed.

11 Claim "Ciproxin causes significantly fewer GI side effects than co-amoxiclav (p <0.004)"

COMPLAINT

SmithKline Beecham pointed out that the reference quoted (Barash 1991) was unavailable from the British Library. The incidence of adverse events found with ciprofloxacin (Ciprofloxacin Monograph 1992) was similar to that found with Augmentin (Neu et al, 1993.) The company pointed out that this reference compared efficacy of a 5 day course of Augmentin and yet in cost comparisons a 7 day course was compared. A breach of Clause 7.2 was alleged.

RESPONSE

Bayer's response was similar to that given in point 6 above.

In addition, Bayer said that the Barash paper deemed a patient evaluable if they had a minimum of five full days treatment and more prolonged courses were permitted. The paper made no reference to treatment costs.

PANEL RULING

The Panel noted that this was similar to point 6 above. In addition the Panel noted that the data sheet for Augmentin did not recommend a course duration. The Panel considered that as in point 6 above the claim was accepable and its ruling of no breach of the Code would also apply to point 11.

12 Claim "Ciproxin dosage is more convenient than co-amoxiclav - bd for 5 days vs tds for 7 days"

COMPLAINT

SmithKline Beecham pointed out that the Augmentin data sheet did not recommend a course duration. Therefore, in a comparison of costs, it was more appropriate to compare on a cost per day basis. A breach of Clause 7.2 was alleged.

RESPONSE

Bayer submitted that pack sizes and market research supported the claim. Co-amoxiclav was supplied in blister strips of 21 tablets, ciprofloxacin in strips of 10 tablets. Less than seven day courses of co-amoxiclav were merely dispensed loose from bulk. Taylor Nelson (Feb 1995) provided information 'Anti-infectives - Dosage, Regimen and Length of Therapy'. For chest infections, the subject of

Bayer's leavepiece, Taylor Nelson recorded that for co-amoxiclav 375mg, 74% of 9516 patients were prescribed a seven day course, 18% a five day course. With 625mg co-amoxiclav, 86% were prescribed a seven day course for chest infections. With 500mg ciprofloxacin, 68% were prescribed a five day course, 21% a seven day course.

Bayer said that SmithKline Beecham must have its reasons for marketing a seven day blister pack, and most antibiotic labelling entreated the patient to "complete the prescribed course unless otherwise directed". It was clear that a twice daily regimen carried greater potential for compliance than a three times daily regimen and the greater convenience of the former when claimed did not constitute a breach of Clause 7.2. Bayer submitted that from the research above, a cost comparison of 5 days ciprofloxacin against 7 days co-amoxiclav was entirely justified (point 11.)

PANEL RULING

The Panel noted that there was no comparison of cost in the leavepiece.

The Panel noted that Augmentin was supplied in a 21 tablet pack which at a dose of three tablets a day would provide a seven day course. There was no course duration for Augmentin but, given its packaging, it was not unreasonable for Bayer to refer to a seven day course. In the Panel's view the twice daily dose of Ciproxin for five days would be seen as more convenient than a thrice daily dosing schedule for five or seven days. The claim was not unreasonable and the Panel ruled no breach of the Code.

D JOURNAL ADVERTISEMENT

The journal advertisement was headed "Sense and Sensitivity" and appeared in an advertorial format. The advertisement was targeted at general practitioners and had been published in Pulse, GP and the British Medical Journal. It had also been provided to GP representatives. There were two allegations, both of which concerned a section headed "Maintaining sensitivity to antibiotic therapy".

13 Use of data from blood culture isolations

This allegation concerned statements that *Haemophilus influenzae*, from blood culture isolates, had maintained its sensitivity to ciprofloxacin between 1989 and 1994 whereas other therapeutic options, such as co-amoxiclav, experienced increasing bacterial resistance. This was followed by a chart comparing the percentage *H influenzae* resistance for co-amoxiclav and ciprofloxacin.

COMPLAINT

SmithKline Beecham alleged that it was misleading and irrelevant to use *H influenzae* blood isolate resistance data in support of respiratory tract infection in the community. By clinical definition, patients having blood cultures tended to be more seriously ill. Therefore, blood culture data was not likely to be fully representative of *H influenzae* resistance in the community. A breach of Clause 7.2 was alleged.

RESPONSE

Bayer submitted that data from more seriously ill patients was completely valid. By specifying the population with the bacteraemia studied, Bayer had made it clear to whom it was referring. There was no attempt to mislead.

PANEL RULING

The Panel accepted Bayer's response that it would be clear to readers that blood culture isolates had been used for the sensitivity tests. The Panel therefore ruled no breach of the Code.

14 Comparison of sensitivity to *S pneumoniae*

COMPLAINT

SmithKline Beecham drew attention to the paragraph which appeared immediately below the material at issue in point 13 above.

SmithKline Beecham stated that with reference to *S pneumoniae* the advertisement stated "...this increasing resistance is often the reason why first-line antibiotics fail to work in these patients." This claim should have been referenced.

The Alexander Study (JAC 1996) showed 95% sensitivity of *S pneumoniae* to amoxycillin/co-amoxiclav indicating that this organism was highly sensitive to amoxycillin and Augmentin. It was therefore misleading to suggest that Augmentin/amoxycillin would fail to work as a result of low 4-5% resistance.

The following excerpt (Alexander Study JAC 1996 - Gruneberg et al) summarised:

> "Quinolones are not generally considered agents of choice for pneumococcal infection: failures have been reported following ciprofloxacin therapy (Cooper & Lawler, 1989; Lee *et al*, 1991.) The quinolones display MIC90 values too close to their maximum achievable serum concentrations to warrant a high ranking. Examination of the intrinsic in-vitro activity (mode MIC and MIC90) reveal that the most potent agents overall against *S pneumoniae* were the b-lactams: amoxycillin, amoxycillin/clavulanate, ceftriaxone and cefuroxime".

In contrast, the ciprofloxacin data sheet stated that *'ciprofloxacin is less active'* against organisms which include *S pneumoniae* and goes on to suggest that *"...sensitivity testing should be performed before treatment is commenced"*. Curiously, Bayer had overlooked these guidelines. A breach of Clause 7.2 was alleged.

RESPONSE

Bayer said that the final paragraph of the relevant section clearly referred to penicillin and erythromycin. It was totally unrelated to the paragraph which appeared above it which was the subject of point 13.

The Communicable Disease Review, as referenced in the advertisement, stated.

> "The rates of pneumococcal infections reported in very young and elderly people have risen much more

rapidly and, although this observation may be artefactual, it may be associated with an observed increase in reports of antibiotic resistance"

"Increasing numbers of pneumococcal isolates are resistant to one or more of the antimicrobials commonly used to treat this infection"

"It is possible, however, that the increased rate of reported infection may be caused by decreasing antibiotic sensitivity of pneumococci"

"The pattern reported here is more representative of the resistance of infecting organisms in hospital patients and confirms the trend of increasing resistance to penicillin and erythromycin".

The paragraph in question did not mention co-amoxiclav or any SmithKline Beecham product.

Bayer said that SmithKline Beecham's comments on the Alexander study were pertinent and undisputed but were not relevant, as there was no claim for ciprofloxacin and pneumococcal infection. Bayer was very aware of the sensitivity testing issue, but it did not have to appear in every piece of promotional text, when it was prominently stated in the abridged prescribing information.

PANEL RULING

The Panel noted as in point 3 above that there was no need to reference the claim as it did not refer to a published study. The Panel did not consider that the section was unreasonable and there was no mention of co-amoxiclav. The Panel therefore ruled no breach of the Code.

Complaint received 2 December 1996

Case completed 13 March 1997

CASE AUTH/480/12/96

EVANS v AURUM

Promotion of adrenaline injection

Evans Medical complained about the promotion of adrenaline injection in a prefilled syringe by Aurum.

The Panel ruled that a claim that the Aurum product was "The only ready to use adrenaline...." was misleading. The Appeal Board overturned the Panel's ruling on appeal by Aurum. The Aurum product was the only ready to use adrenaline in a prefilled syringe as the Evans product required that two components be assembled before use. No breach was ruled.

The Panel ruled that a claim "Quicker to use - No prior assembly required, simply expel bubble & connect to line" was not a hanging comparison as the comparison was between Aurum's product and all products that needed prior assembly. The Appeal Board upheld the Panel's ruling following an appeal from Evans.

The Panel ruled a breach as the prescribing information had not included the cost. No breach was ruled regarding allegations that claims "Special luer attachment" and "AURUM The Gold Standard" could not be substantiated.

Evans Medical Limited complained about the promotion of adrenaline injection in a prefilled syringe by Aurum Pharmaceuticals Ltd. Aurum Pharmaceuticals was not a member of the ABPI but had nevertheless agreed to having the complaint considered under the Code.

The material at issue was a one page sheet which listed features of the adrenaline for injection on one side with the summary of product characteristics printed on the reverse. There were five allegations which were considered as follows:-

1 Claim "The only ready to use adrenaline 1mg in 10ml prefilled syringe for CPR"

COMPLAINT

Evans pointed out that its Minijet product, was a prefilled syringe with 1mg adrenaline in 10ml. It was supplied ready for use. Evans alleged that the claim was in breach of Clauses 7.2, 7.3, 7.8 of the Code.

RESPONSE

Aurum pointed out that Evans' Minijet was a multicomponent system which consisted of two main parts. Each had a protective cap which had to be removed before assembly. The component parts were a vial and a plastic vial injector. To use the system it was necessary to remove the cap from the vial, remove the cap from the plastic vial injector, insert and screw the vial into the plastic vial injector and remove the luer tip cover. Only then was it ready to use. Aurum submitted that with the number of stages required to assemble the Minijet, it could be argued that an ampoule of adrenaline and a plastic disposable syringe could be classed as ready to use. Aurum provided a copy of the instruction sheet for the Minijet.

Aurum's product came in a prefilled syringe of standard design requiring no prior assembly. It was therefore ready to use. No other companies supplied adrenaline syringes of this strength in the UK.

PANEL RULING

The Panel considered that the phrase "ready to use" would be taken to mean that minimal manipulation of the equipment was necessary before an injection could be given. Clearly the Aurum product was more "ready to use" than the Evans product which required fitting together before use. The product was being promoted for

use in cardiopulmonary resuscitation (CPR). The Panel had some concerns about the use of the term "The only" as the Evans Minijet product was certainly more "ready to use" than a syringe and ampoule. On balance, the Panel considered the Aurum claim to be misleading and ruled a breach of Clause 7.2 of the Code.

APPEAL BY AURUM

Aurum pointed out that the Panel had accepted that the Aurum product was ready to use, but also that the Evans Minijet product and an ampoule of 1mg/1ml adrenaline + diluent + disposable syringe were also ready to use with various levels of manipulation. Clearly, as one moved down the list, the products became increasingly unsuitable for CPR. They remained however "ready to use" according to the Panel which in Aurum's view was not a valid definition, for CPR products in particular. It was a product-oriented definition, not use-oriented.

Aurum submitted that to apply a judgement of what was "reasonable" in describing a product as ready to use was surely contentious, and therefore should be avoided. The non contentious way to make the decision was to ask what the medical practitioner needed. In this case, he/she was usually presented with a patient with an iv line in place, through which line he/she had to deliver the adrenaline. Therefore the need was for a glass prefilled syringe which could be directly connected to the central line to administer the dose.

Evans Medical's Minijet cartridge system had to be assembled before use. Therefore, only the Aurum prefilled syringe met this criterion, so the claim was justified. The complaint did not originate from CPR healthcare personnel. The claim was understood by the medical profession, and in no way was likely to wrongly affect their judgement.

Samples of the Aurum product and the Minijet system were provided. The Minijet system was available on the market before the Aurum prefilled syringe became available.

APPEAL BOARD RULING

The Appeal Board noted that the claim at issue "The only ready to use adrenaline 1mg in 10ml prefilled syringe for CPR" referred to the Aurum product as being available as a prefilled syringe. In the Appeal Board's view, the Minijet system was not a prefilled syringe. The Aurum product could be used immediately whereas the Minijet system required intervening steps as the two components had to be assembled before use. The Appeal Board did not consider that the claim was misleading and therefore ruled no breach of the Code.

The appeal on this point was therefore successful.

2 Claim "Quicker to Use"

This claim appeared in a stab point "Quicker to use - No prior assembly required, simply expel bubble & connect to line".

COMPLAINT

Evans alleged that the phrase "Quicker to use" was a hanging comparative in breach of Clause 7.2 of the Code.

RESPONSE

Aurum said that Clause 7.2 of the Code was specific in relation to hanging comparisons referring to medicines. It was not making any claim in relation to adrenaline acting more quickly, only that its prefilled syringe was quicker to use. The Aurum syringe was designed for use in CPR and speed of use in this acute clinical situation could be potentially life saving. It was considered by the growing number of hospitals that used its prefilled syringes that Aurum's product offered a significant advantage over alternatives. If this was not the case, ampoules would be used more widely.

The remainder of the claim "no prior assembly required, simply expel bubble & connect to line" was the reason why the product was self evidently quicker to use. Were the company to specify the Minijet as the comparator, it would have been in breach of the Code. The target audience would fully comprehend the comparison by virtue of the qualification.

PANEL RULING

The Panel did not accept that Clause 7.2 only related to hanging comparisons referring to medicines. The Code applied to all information in advertisements and not simply to actual references to medicines.

The Panel's view was that the claim "Quicker to use" was a comparative term. The comparator was not identified as such but, in the Panel's view, would be taken to be other products where prior assembly was required. The Panel considered that, given the context, the claim was not a hanging comparison and ruled no breach of the Code.

APPEAL BY EVANS

Evans Medical said it was clear from Aurum's response that the claim "Quicker to use" was intended to imply an advantage over alternative delivery systems, including the Minijet presentation. Evans accepted that the Aurum product required no prior assembly but pointed out that the Minijet device could be assembled in about 3 seconds. When one considered the time involved in unpacking, connecting the device to an indwelling cannula, and delivering the drug to the patient, the company believed that in practical use there was unlikely to be any significant difference in speed of use between the two devices.

Staff involved in cardiopulmonary resuscitation were trained specifically in the use of Minijet and could unpack, assemble and deliver the medicine to the patient within a few seconds. The time saving over syringe and ampoule systems had been studied and Evans' view was that the Aurum device offered no significant time saving and hence no clinical benefit.

The supplementary information to Clause 7.2 clearly required any comparator to be stated rather than implied as in this case. It was surprising that the Panel considered a comparative term without a stated specified comparator not to be a hanging comparison.

RESPONSE FROM AURUM

In its initial response Aurum pointed out that Evans had omitted the second half of the claim which qualified the claim. Aurum referred to its original submission which was accepted by the Panel.

Evans was not appealing against the Panel's judgement, but rather raising new issues relating to the qualification, and providing unsubstantiated data concerning the time taken to assemble the Minijet. This was not a valid appeal against the original complaint.

FURTHER COMMENTS FROM EVANS

Evans reiterated its view that the claim "Quicker to use" was a hanging comparative. The qualification "no prior assembly required" was irrelevant since assembly was not necessarily the rate limiting step in the use of these products. In Evans' view it was inconceivable that in practice the Aurum product would offer any significant time saving over the Minijet presentation.

It was not clear to Evans from Aurum's responses whether it intended the comparator to be ampoules or Minijets. If the former, then the qualification was not sufficiently specific, as the Minijet could be classed as a product requiring assembly. If the latter, then the claim breached Clause 7.2 as it was not a fair reflection of current practice, for the reasons set out in Evans' appeal. In either case Aurum's claim could hardly be described as unambiguous.

APPEAL BOARD RULING

The Appeal Board accepted that the claim "Quicker to use - No prior assembly required, simply expel bubble & connect to line" implied that the comparison was between Aurum's product and all products that needed prior assembly. The Appeal Board agreed with the Panel that the claim was not a hanging comparison and upheld the Panel's ruling of no breach of the Code.

The appeal on this point therefore failed.

3 Claim "Special luer attachment - No lock required"

COMPLAINT

Evans alleged that this claim implied that the product had some particular merit over normal syringes. If this could not be substantiated, then the claim was in breach of Clause 7.8 of the Code.

RESPONSE

Aurum said that the syringes it used had a special ceramically coated luer which afforded a extremely firm connection, first to the tip cap, and in use to the venflon of an established line. This was indeed a particular merit over normal syringes. Plastic syringes/plastic vial injector did not have this coating and therefore the Minijet being plastic had to have a luer lock or in situ needle.

PANEL RULING

The Panel accepted that the Aurum syringe with its luer fitting did have a special merit and this was capable of substantiation. The Panel therefore ruled no breach of Clause 7.8 of the Code. The Panel did consider, however, that the claim could have been better phrased. The term "luer" represented a size rather than a surface finish.

4 Price

COMPLAINT

Evans alleged that there was no price given in the prescribing information in breach of Clause 4.1 of the Code.

RESPONSE

Aurum accepted that the omission of the price was an error on its part. The company had printed the entire summary of product characteristics (SPC) on the relevant sheet which did not include the price. The company agreed to rectify this on reprint. All its customers had been advised of the price.

PANEL RULING

The Panel ruled a breach of Clause 4.1 of the Code as the price had been omitted. It should be pointed out to Aurum that Clause 4.1 did not require the full SPC to be provided but, in certain respects, only a succinct summary of it.

5 Statement "Aurum The Gold Standard"

COMPLAINT

Evans alleged that the statement "AURUM The Gold Standard" in conjunction with the company's logo which appeared at the bottom of the piece of promotional material in question, constituted a superlative claim which was not capable of substantiation. A breach of Clause 7.2 of the Code was alleged.

RESPONSE

Aurum said that it had used this statement as a "sign off "on promotional material since it started trading some four years ago. It also used the statement on non product related corporate items. The company pointed out that there was of course an obvious connection in that Aurum was the Latin for gold. "The Gold Standard" referred to a monetary standard which might be exceeded and in no way represented a superlative. It was considered as a standard to which the company aspired in providing overall service to its customers. The statement was clearly separated from product related claims.

PANEL RULING

The Panel considered that the expression "The Gold Standard" was not a superlative but it could be regarded as an exaggerated or all-embracing claim. In the present instance, however, there were two factors to be considered. One was that the expression related to the name of the company rather than the product and the

other was that the word "aurum", which was used as the name of the company, was the Latin word for gold. In these circumstances, the Panel did not accept that the statement "Aurum The Gold Standard" was unreasonable. The Panel therefore ruled no breach of the Code.

Complaint received	**2 December 1996**
Case completed	**13 March 1997**

CASE AUTH/482/12/96

GLAXO WELLCOME v ASTRA

Booklet on inhaled corticosteroids

Glaxo Wellcome complained that a booklet on inhaled corticosteroids issued by Astra made misleading comparisons between budesonide and fluticasone and did not reflect the most up to date information available.

The Panel was concerned that the title of the booklet gave the impression that it dealt with all inhaled corticosteroids whereas it only discussed two. In addition it was not made clear that much of the data presented had been taken from healthy volunteers and so did not relate to the clinical situation. The Panel considered that it had not been made sufficiently clear that unlicensed doses of both fluticasone and budesonide had been used. Undue emphasis was given to the adverse effects of very high doses of fluticasone while the effects of licensed doses of the medicine were not prominently reported. The Panel noted that the direct comparisons reported between budesonide and fluticasone had not always been between therapeutically equivalent doses of the two medicines. The Panel ruled that the way in which the data had been presented was misleading in breach of the Code.

The Panel noted that publications referred to by Glaxo Wellcome as representing the most up to date information had not been available either at the time the booklet was published or during the time it was used by Astra and ruled no breach of the Code in that regard.

Glaxo Wellcome UK Limited complained about an eight page A5 booklet entitled "Supression of HPA function by inhaled corticosteroids: An update" issued by Astra Pharmaceuticals Limited. The booklet had the appearance of a scientific discussion on the topic. Pages two and three of the booklet gave an overview of five studies (three of which had been presented at a recent European meeting) that had examined adrenal suppression with fluticasone (Glaxo Wellcome's product Flixotide) alone or in comparison with budesonide (Astra's product Pulmicort). Each of the following four pages gave a resumé of one particular study (Dogterom *et al*; Clark *et al*; Grahnen *et al*: Trescoli-Serrano and Ward). Three of the studies, Dogterom *et al*, Grahnen *et al* and Trescoli-Serrano and Ward, were carried out on healthy subjects. The Clark study was carried out in mild asthmatics. The outer back cover of the booklet (page 8) carried the prescribing information for Pulmicort Inhaler and Pulmicort Turbohaler.

The booklet was prepared in December 1995 and used until March 1996. It was distributed primarily to doctors via Astra's medical representatives.

Glaxo Wellcome complained that the booklet in its entirety was in breach of Clause 7.2 of the Code as it made misleading comparisons between budesonide and fluticasone. Glaxo Wellcome made three specific allegations.

1 The extrapolation of healthy subject data to the clinical situation

COMPLAINT

Glaxo Wellcome said that the healthy volunteers in the study by Trescoli-Serrano and Ward were exposed to single nocturnal doses of up to 4000mcg of fluticasone which was four times greater than its maximum licensed single dose (1000mcg twice daily). Plasma cortisol levels were measured the following morning to assess the effect upon the HPA (hypothalamic-pituitary-adrenal) axis.

Glaxo Wellcome said that undue emphasis was placed upon the adverse effects of the unlicensed doses of fluticasone with only a passing reference being made to the insignificant effect of the only dosage within the licensed range which was used in the study.

Glaxo Wellcome alleged that this unbalanced presentation of the results from a study using clinically irrelevant doses of fluticasone in healthy volunteers was in breach of Clause 7.2 of the Code.

RESPONSE

Astra submitted that it had made no attempt to extrapolate data and noted that Glaxo Wellcome cited no evidence to support this. Each study summary clearly stated whether healthy subjects or patients were used. It was customary to evaluate drug safety in healthy subjects to avoid the confounding effects of previous and concomitant therapy.

The booklet summarised the study by Trescoli-Serrano and Ward without introducing emphasis on any particular dose. Astra accepted that one of the doses of fluticasone used in the study was outside the licensed daily range and this was emphatically stated using bold typeface of the same font size on the relevant page. Astra believed that selective omission of study data would in itself be misleading.

PANEL RULING

The Panel was concerned that while the title of the booklet

was "Suppression of HPA function by inhaled corticosteroids: An Update" the contents only examined suppression of HPA function with two corticosteroids - fluticasone and budesonide. In addition, the first sentence in the booklet stated that studies presented at a recent meeting had questioned the safety profile of fluticasone. The Panel considered that this opening statement would be taken by many of the intended audience to refer to the clinical situation. Given that two of the three studies presented were in healthy volunteers the Panel considered that the statement might mislead readers as to the clinical significance of the ensuing data. The Panel noted that Clark *et al* had prefaced their study with the statement that, in theory, fluticasone and budesonide might be better absorbed from healthy lungs than from the lungs of asthmatics. This would mean that studies conducted in healthy volunteers might overestimate cortisol depression in absolute terms.

The Panel noted that the licensed single doses for fluticasone ranged from 100mcg - 1000mcg (0.1mg - 1mg), while those for budesonide were 200mcg - 800mcg (0.2mg - 0.8mg). Each medicine could be given twice daily. The Trescoli-Serrano paper detailed twelve healthy subjects who were given single doses of fluticasone of 1, 2 and 4mg by Diskhaler and 2mg and 4mg by metered dose inhaler (MDI). The Panel noted that the 1mg dose was the only licensed single dose of fluticasone.

The Panel noted that in the overview on pages two and three of the booklet, reference was made to the Trescoli-Serrano study. The overview stated that "Cortisol suppression with both doses [2mg and 4mg] from the MDI was statistically significant". Similarly the 2mg and the 4mg doses from the Diskhaler also significantly reduced morning plasma cortisol. No mention was made, however, of the 1mg Diskhaler dose which had no significant effect in this regard. At the end of the overview, below the references on page 3, was a statement in small bold type which read "NB. The maximum recommended adult doses are 2000mcg/day for fluticasone ... and 1600mcg/day for budesonide". There was no indication that these were total daily doses and had to be given in divided doses.

In the resumé of the study on page 7, there was a statement in bold, although in a type size no bigger than the rest of the text, at the bottom of the page, which read "NB The higher doses (4mg) are outside the recommended range for [fluticasone]". The Panel noted that 2mg, as a single dose, was similarly not within the licence. The conclusion of the study stated that a dose related fall in cortisol suppression had been demonstrated.

The Panel was concerned about the use of doses outside the licence for both Astra's product Pulmicort and Glaxo Wellcome's product fluticasone. Given, however, that the booklet was a scientific report of a number of studies, rather than a straightforward promotional item, it was not unreasonable to refer to unlicensed doses but this needed to be made very clear so that readers could adequately assess the clinical significance of any data presented. The Panel considered that the statements on pages 3 and 7 regarding the licensed dose of fluticasone were inadequate in terms of prominence because, although in bold, the print size was very small and inaccurate in that 2mg as a single dose was outside the product licence for fluticasone. Both the resumé and the overview failed to point out that the maximum licensed single dose of fluticasone (1mg) failed to significantly decrease morning cortisol levels.

The Panel considered that overall the way in which the data had been presented was misleading and ruled a breach of Clause 7.2 of the Code.

2 Inappropriate microgram for microgram comparisons and the failure to use the most up to date references

COMPLAINT

Glaxo Wellcome said that the study performed by Dogterom *et al*, again in healthy volunteers, compared the effects upon HPA function of similar microgram doses of budesonide and fluticasone taken twice daily over four days. The abstract of this Astra sponsored study stated that budesonide and fluticasone were given at "equivalent therapeutic doses" and this statement was quoted in the Astra booklet. However, reference to the data sheet for Flixotide (fluticasone) stated that "Equivalent disease control is usually obtained at half the daily dose of other currently available inhaled steroids". Glaxo Wellcome alleged that the statement in the Astra document was therefore misleading in breach of Clause 7.2 of the Code. The study had now been published in full, under revised authorship, and the reference to "equivalent therapeutic doses" was no longer present. In view of the full publication of this study, the document no longer represented the most up to date information available and so was in breach of Clause 7.2 of the Code.

The study by Grahnen *et al* on healthy volunteers again directly compared the effects upon HPA function of doses of budesonide and fluticasone which were not therapeutically equivalent when used in asthmatic patients. The results of this study were in contrast with a twelve week study by Ringdal *et al*, comparing the efficacy and systemic activity of fluticasone 400mcg twice daily and budesonide 800mcg twice daily using the same devices as in the Grahnen study. In Ringdal's study, fluticasone was more effective than budesonide at these doses in improving mean morning peak expiratory flow with significantly less effect upon mean morning plasma cortisol levels, which remained within the normal range for both drugs.

Glaxo said that the Astra document was misleading in comparing the "systemic potency" of inappropriately matched dosages of fluticasone and budesonide in healthy volunteers, when the relative clinical efficacy of fluticasone and budesonide was not mentioned, in breach of Clause 7.2.

RESPONSE

Astra submitted that Glaxo Wellcome's complaint that it had made inappropriate microgram for microgram comparisons appeared to be based on a misunderstanding of how the relative potency of drugs was established.

The accepted method for establishing relative drug potency (for either efficacy or systemic effect) was to compare doses which produced similar or equal effect.

This was conventionally done by measuring responses to a wide range of doses and comparing the relationship for each drug (dose response relationship). Relative potency was calculated from the separation of the individual log dose response plots and was therefore not derived by comparing any single dose. This method was used in the studies by Dogterom and Grahnen.

Dogterom compared three doses each of fluticasone and budesonide using metered dose inhalers. Astra accepted that there was evidence that when given in this way fluticasone was twice as potent as budesonide regarding antiasthma effects and could be used at half the dose. However, Dogterom reported that fluticasone was approximately four times more potent than budesonide regarding systemic effects (HPA suppression). This meant that when equivalent therapeutic doses (eg 400mcg/day fluticasone and 800mcg/day budesonide) were compared in healthy subjects the systemic effects of fluticasone were greater. The quotation "at equivalent therapeutic doses, [fluticasone] shows a significantly greater cortisol suppression than budesonide" was clearly substantiated by the data.

Astra said that the full version of this study was published in July 1996 (the booklet in question was not distributed after March 1996) and thus Glaxo Wellcome's claim that it had failed to use the most up to date references could not be substantiated.

The study by Grahnen compared four doses each of fluticasone and budesonide using dry powder devices (Diskhaler and Turbohaler respectively). In this situation fluticasone was not clinically effective at half the dose of budesonide. This was because a Turbohaler delivered approximately twice as much drug to the lungs as a metered dose inhaler enabling the dose of budesonide to be halved. This was acknowledged in the draft new British Thoracic Society Guidelines and was upheld an Appeal Board ruling in May 1995. The net result was that when a budesonide Turbohaler was used, budesonide and fluticasone had equivalent clinical efficacy on a microgram basis. This had been shown in clinical studies which had compared budesonide Turbohaler with fluticasone Diskhaler.

Grahnen found that the systemic potency of fluticasone Diskhaler was 1.7 times greater than budesonide Turbohaler. Thus when equivalent clinical doses were used the effect of fluticasone in healthy subjects was greater. This was true across the range of doses used in the study.

Astra pointed out that the Ringdal study had not been published during the time of use of the booklet in question.

Astra did not accept that the doses of fluticasone and budesonide used in these studies were inappropriately matched since in each case a range of doses was used. The conclusions that the systemic effect of fluticasone in healthy subjects was greater than budesonide were clearly substantiated by the data. Astra said that its booklet was a summary of the scientific data presented at the meeting and accurately reflected the data.

PANEL RULING

The Panel noted that the study by Dogterom *et al* was in healthy volunteers each of whom received fluticasone 200mcg, 375mcg and 1000mcg twice daily. The doses of budesonide to which these were directly compared were 200mcg, 400mcg and 1000mcg twice daily respectively. The Panel noted that both medicines were given by metered dose inhaler and that with this route of administration it was accepted that the dose of fluticasone, in terms of micrograms administered, could be half that of the other corticosteroid. The Panel noted that Astra had accepted this point. The Panel accepted Astra's submission that a wide range of doses of each medicine had to be tested but considered that the direct comparisons reported had not been between therapeutically equivalent doses but between microgram equivalent doses the clinical relevance of which was unclear. To confuse these two issues was misleading and the Panel ruled a breach of Clause 7.2 of the Code.

The Panel noted that the Grahnen study was also in healthy volunteers each of whom received fluticasone 100, 200, 500 or 1000mcg twice daily via a Diskhaler. Budesonide 100, 200, 400 or 800mcg was administered twice daily via a Turbohaler. The Panel noted Astra's submission that given these routes of administration both corticosteroids were accepted to be therapeutically equivalent on a microgram for microgram basis. The resumé of the study concluded that cortisol suppression was greater for fluticasone than for budesonide but failed to point out that this was only the case for the higher doses. There was little difference in cortisol suppression when fluticasone and budesonide were both administered in doses of 100 or 200mcg twice daily. The Panel considered that the conclusion was misleading with respect to lower doses of fluticasone and ruled its use to be a breach of Clause 7.2 of the Code.

The Panel noted that the full report of the Dogterom abstract had been published in July 1996 and that the Ringdal study had been published in late 1996. The booklet in question had not been used after March 1996. The allegation that Astra had failed to use up to date material was, therefore, unfounded and the Panel ruled no breach of the Code in this respect.

3 Selective use of data and use of unlicensed doses

COMPLAINT

Glaxo Wellcome said that the report on the study by Clark *et al* was prefaced by the comment that other comparisons of the systemic effects of fluticasone and budesonide had been in healthy subjects when better absorption of drugs from the lung might take place compared with that in asthmatic subjects, resulting in greater absolute HPA suppression. However, the effects of single nocturnal doses of fluticasone were then compared with similar microgram doses of budesonide rising to twice the maximum licensed single dose, in twelve patients who had very mild asthma and whose average pre-study daily dose of inhaled steroid was 208mcg of beclomethasone dipropionate, one patient taking no inhaled steroid at all. These patients then received doses of 500, 1000, 1500 and 2000mcg of fluticasone when the typical starting dose for severe asthma was 500 - 1000mcg taken twice daily. The selectively quoted data in the document did not reveal

that the licensed doses used in the study showed no significant differences in their effects upon morning serum cortisol and plasma ACTH levels. While there was an apparent reduction in overnight urinary cortisol with 500mg of fluticasone compared with 400mcg of budesonide, the results for the 1000mcg dose were "not given", although the text mentioned that there was no difference between the results for fluticasone and budesonide. Glaxo Wellcome said that the Astra booklet once more highlighted the effects of out of licence dosages (1500 and 2000mcg).

Glaxo Wellcome alleged that this was misleading and in breach of Clause 7.2 of the Code in stressing the systemic effects of clinically inappropriate doses of fluticasone in patients with mild asthma. In addition, this study was published in full in March 1996 which again meant that the booklet did not reflect the most up to date information available.

Glaxo Wellcome said that while Astra had put various caveats at the foot of some pages of the booklet regarding the recommended adult daily doses of fluticasone, it considered them to be quite inadequate as they did not point out that the maximum licensed dose of fluticasone was 1000mcg twice daily, not 2000mcg daily. The latter could easily mislead the reader into believing that a single dose of fluticasone of 2000mcg was acceptable. Glaxo Wellcome alleged that this was misleading and in breach of Clause 7.2 of the Code.

RESPONSE

Astra submitted that the Clark study compared a range of doses (four each of fluticasone and budesonide), both within and out of licence. It was customary to evaluate drug safety using a broad range of doses including higher than licensed doses. Licensed doses for fluticasone and budesonide were broadly similar and this was reflected in the choice of doses used in the study.

Astra said that it was not the case that it had selectively quoted data from this study. The abstract contained no numerical values for 1000mcg/day, but stated that for urinary cortisol the difference was not statistically significant. The study summary accurately reflected this.

The study by Clark was published in full during March 1996. The booklet had not been used since that time. Astra said that the allegation that it had failed to use the most up to date references could not therefore be substantiated.

Astra submitted that the study summary did not stress the systemic effects of clinically inappropriate doses of fluticasone but was an accurate and scientifically sound comparison of the effects of both budesonide and fluticasone on the HPA axis. The booklet was a summary of the scientific data presented at the meeting.

Astra did not accept that the booklet in any way encouraged use of products outside the product licences. It was regular practice to quantify inhaler steroids by total daily dose. No attempt was made to recommend any particular dosage regimen of any product in what was then an update of recently presented studies. Astra had clearly pointed out where out of licence use had occurred. It would have been misleading and poor science to selectively edit data on these grounds. As required by the Code, prescribing information was provided for budesonide.

PANEL RULING

The Panel noted that in the study by Clark *et al* mild asthmatics had been given single doses of fluticasone 500, 1000, 1500 and 2000mcg. Single doses of budesonide 400, 1000, 1600 and 2000mcg had also been administered. Both medicines had been given by a metered dose inhaler. The Panel noted that in the overview at the front of the booklet (page 2) readers' attention was drawn to the cortisol suppression with high doses of fluticasone, 1500mcg and 2000mcg, although there was no mention that as single doses of the medicine these doses were both outside the product licence.

The Panel noted that a table of results regarding cortisol suppression was given in the resumé of the study (page 5) although no figures were reported for fluticasone 1000mcg vs budesonide 1000mcg. While the text reported that both medicines had given a similar response and were not statistically different from one another at these doses, this information was not as immediately obvious to readers as it would have been if the figures had been included in the table. In addition the study resumé failed to point out that fluticasone 1500mcg and 2000mcg were not licensed as single doses of the medicine.

The Panel noted that when both were given by metered dose inhaler fluticasone could be given at half the dose of budesonide. The study resumé concluded that fluticasone exhibited greater adrenal suppression compared with budesonide on a microgram equivalent basis in asthmatics. The clinical relevance of this data was unclear.

The Panel considered that the data, as presented, was misleading and ruled a breach of Clause 7.2 of the Code.

The Panel noted that the full report of the Clark study had been published in March 1996. The booklet in question had not been used after March 1996. The allegation that Astra had failed to use up to date material was, therefore unfounded and the Panel ruled no breach of the Code in this respect.

Complaint received **16 December 1996**

Case completed **4 March 1997**

CASE AUTH/483/12/96

GLAXO WELLCOME v SMITHKLINE BEECHAM

Promotion of Vectavir Cold Sore Cream

Glaxo Wellcome complained about the promotion of Vectavir Cold Sore Cream by SmithKline Beecham. Three promotional items were the subject of complaint and allegations were also made about a press release and about the promotion of Vectavir in the lay press. Most of the matters complained of appeared, *inter alia*, in a detail aid.

Glaxo Wellcome alleged that the claim "Clinically effective - with early or late treatment" was in breach of the Code for a number of reasons. The Panel considered that doctors were being encouraged to prescribe Vectavir to patients presenting with cold sores that had reached an advanced stage and considered that it would be better to define the period during which the product was effective more precisely. It was ruled that the claim was misleading. No breach was ruled in relation to an allegation about initiation of treatment within one hour as SmithKline Beecham had not made such a claim. A breach of the Code was ruled in relation to SmithKline Beecham's failure to supply Glaxo Wellcome with details about how many patients began treatment at each lesion stage in order to substantiate the claim. A further breach was ruled in relation to SmithKline Beecham's definitions of "early" and "late" which were considered to be misleading. An allegation that the claim went outside the scope of the summary of product characteristics was rejected.

A graph comparing the intracellular half-lives of aciclovir and penciclovir triphosphates was ruled to be misleading because of a failure to balance the claim with a reference to the fact that the affinity of the triphosphate for the viral DNA polymerase was one hundred times greater for aciclovir triphosphate than for penciclovir triphosphate. Aciclovir was the active ingredient of Zovirax (Glaxo Wellcome's product) and penciclovir was the active ingredient of Vectavir. No breach of the Code was ruled in relation to an allegation concerning the use of patient assessed data rather than physician assessed data. Similarly, no breach of the Code was ruled in relation to an allegation concerning the statistical versus clinical significance of patient assessed data. Although the advantage for the patient was small, the Panel considered that it would nonetheless be enough to be of significance to patients. A table headed "Results with aciclovir cream. Early treatment" was ruled to be in breach. The Panel considered that the implication of the table was that treatment with aciclovir needed to be started early whereas treatment with Vectavir did not. A breach of the Code was ruled in relation to a claim "Significantly less irritant than aciclovir cream" as the Panel did not consider that it had been adequately substantiated.

The heading of a press release "Setting a new standard in the management of herpes labialis" was considered to be too strong for use in a press release which would be going to the lay press. The implication was that Vectavir was an improvement on other products but no study directly comparing Vectavir and other topical antivirals had been conducted. A statement in the press release "..... by the time patients get to them it is too late to treat with existing topical antiviral agents" was ruled in breach. There was again the implication that Vectavir could be used for patients presenting late, including those with cold sores at the crust stage. The period during which the product was effective needed to be better defined.

The Panel rejected an allegation that the activities of SmithKline Beecham in relation to Vectavir amounted to the advertising of a prescription only medicine to the public. The circumstances did not amount to that. Articles appearing in the media were judged not upon their content but upon what the company concerned or its agent had supplied.

Glaxo Wellcome UK Limited complained about the promotion of Vectavir Cold Sore Cream by SmithKline Beecham Pharmaceuticals. There were three promotional items at issue, these being a representative detail aid (ref: 0696 VC:DA/6/004), a pharmacy information pack (ref: 0696 VC:MF/6/005) and a double page journal advertisement which had appeared in GP (ref: 0696 VC:AD/6/514). Allegations were also made about a press release issued in June 1996 and about the promotion of Vectavir in the lay press. Glaxo Wellcome stated that most of the statements to which it objected appeared in the detail aid and that was accordingly the item primarily referred to.

REPRESENTATIVE DETAIL AID

A "Clinically effective - with early or late treatment"

Glaxo Wellcome said that this claim appeared on the front cover of the detail aid and was central to the entire promotional campaign.

An asterisk against the claim referred to a footnote which stated that "Early treatment is intervention at the erythema or prodrome stage and late treatment is intervention at the papule-to-crust stage (combined data), as defined in clinical trials". The references were "Data on file" and a conference abstract by Spruance *et al.*

Glaxo Wellcome alleged that the claim was misleading and in breach of Clause 7.2 of the Code for the following reasons:

1 Encouragement to prescribe at advanced stage

COMPLAINT

Doctors were being encouraged to prescribe Vectavir to patients presenting when their cold sores had reached an advanced stage, when there was no clinical rationale for treatment. The natural history of cold sores (herpes simplex labialis) was well documented in the literature and might be summarised as follows:

i) Prodromal phase - Tingling, burning and/or itching sensations, lasting from a few hours to one day.

ii) Macule/papule phase - Reddening of the skin (erythema) and appearance of small, raised lumps (papules). This stage lasted for a few hours.

iii) Vesicle phase - Papules enlarge, become filled with fluid and "coalesce" (join together) to form a small discrete collection of blisters (vesicles). The vesicles usually appear by the second day of the cold sore attack.

iv) Ulcer phase - Vesicles coalesce and rupture within a few hours, to produce a painful erosion (ulcer). The ulcer usually appeared by the third day of the cold sore attack.

v) Crust (scab) phase - This represented the healing stage of the cold sore lesion, and was longer in duration than any of the previous phases, often lasting for 7 days or more.

It was an accepted principle that virus replication had ceased by the time the ulcer dried out to form the crust (scab). Therefore, it could not possibly make sense to initiate antiviral therapy as late as the crust stage.

Glaxo Wellcome said that the extent to which the promotional claim "clinically effective - with early or late treatment" was misleading (to both doctors and patients) was well illustrated by SmithKline Beecham's press launch bulletin and subsequent coverage in the medical and lay press. The news release document from the press materials contained the following statements:

> "The launch of Vectavir is timely, as a survey of UK general practitioners (GPs) has found that patients with cold sores often present too late for effective treatment with existing agents. GPs perceive a great need for a new product which is effective both in the early and the late stages of the development of a cold sore."

and

> "Many clinicians are aware of the distress caused to patients by cold sores and they are aware that by the time the patient gets to them it is too late to treat with existing topical antiviral agents. These new data are important in that treatment can now be started at a later stage".

Glaxo Wellcome enclosed some examples of subsequent press coverage which showed how these statements were interpreted by medical journalists. Glaxo Wellcome said that these examples clearly illustrated the misleading nature of the claim in question.

RESPONSE

SmithKline Beecham said that it had defined "early" treatment of a cold sore as intervention at the prodrome or erythema stage and "late" treatment as intervention at the papule stage or later. These definitions of "early" and "late" stages of a cold sore had been used by Professor Spruance, a leading physician in the herpes labialis field. In addition, the same definitions had been used in a study of oral aciclovir in herpes labialis in which "early" was defined as prodrome or erythema and "late" was defined as papule stage. The use of these terms had specific connotations in this condition in a similar way to the terms "mild" or "moderate" used in hypertension, for example. These were discrete phases within the specific natural history of each condition and encompassed a number of time or "stage" variables.

RULING

The Panel considered that doctors were being encouraged to prescribe Vectavir to patients presenting with cold sores that had reached an advanced stage. There was no clinical basis for using the product at the crust stage although the implication of the qualification ".... late treatment is intervention at the papule-to-crust stage....." was that treatment could be started at the crust stage. It would be better to define the period during which the product was effective more precisely. It was considered that the claim was misleading and a breach of Clause 7.2 was ruled.

The Panel did not consider that the qualifying footnote which indicated what was meant by "early" and "late" treatment was sufficiently prominent and asked that its views in this regard be conveyed to SmithKline Beecham.

Further allegations in relation to the claim "Clinically effective - with early or late treatment" are dealt with in points 2 to 5 below.

2 Initiation of treatment within one hour

COMPLAINT

The trial protocol described by Spruance *et al* required patients to self-initiate treatment within one hour of noticing the first signs or symptoms of a cold sore. Glaxo Wellcome had been unable to ascertain from SmithKline Beecham exactly how many patients actually initiated treatment within one hour, despite having repeatedly requested this information. This represented breaches of Clauses 7.1 and 7.4 in that it constituted failure to provide information and substantiation for a promotional claim.

There appeared to be no data whatsoever to show that Vectavir had any effect if started later than one hour after noticing the first signs or symptoms of a cold sore, and therefore the promotional materials for the product should reflect this.

RESPONSE

SmithKline Beecham said that it had made no promotional claims based on initiation of treatment within one hour and it believed that the lesion stage at initiation of therapy was a more clinically relevant parameter.

The intention of the clinical trials with Vectavir Cold Sore Cream, that patients should initiate treatment within one hour of first noticing signs or symptoms of herpes labialis, was merely to encourage treatment as early as possible.

SmithKline Beecham had not withheld any information from Glaxo Wellcome on this point. SmithKline Beecham was not able to confirm the time of lesion onset in the study population, since this was not a study endpoint. However, considering the natural history of this disease it was highly unlikely that those patients who initiated treatment during the papule or vesicle stages did so within one hour of prodrome onset.

PANEL RULING

The Panel noted that SmithKline Beecham had not made

any promotional claim based on initiation of treatment within one hour and was therefore not required to provide substantiation for such a claim. No breach of the Code was ruled.

3 Lesion stage on entry into clinical study

COMPLAINT

When asked to provide a breakdown of lesion stage on entry into the Spruance study for all patients, SmithKline Beecham provided the "overall" figures, showing that very few patients started treatment at the ulcer or crust stages (2% of the 44% "late" treaters). Glaxo Wellcome therefore questioned how a claim for efficacy at the ulcer or crust stage could be derived from these data. The claim in question therefore also constituted a breach of Clause 7.3 in that it was not substantiable.

Glaxo Wellcome said that it was important to ascertain how many patients began treatment at each of the lesion stages, in each of the treatment groups (Vectavir and placebo). It was possible that the analysis of "early" versus "late" treatment was carried out retrospectively, once the study results had been obtained. If this were the case, it would constitute a subgroup analysis, with loss of the original randomisation and possible introduction of bias (for example, more "late" treaters in the placebo group). However, despite requesting "the full data set from this study", "the early and late sub-group demographics according to treatment", and "how many patients initiated therapy at each and every lesion stage in the treatment and placebo groups", Glaxo Wellcome had still not received this information. It therefore alleged that this also represented breaches of Clauses 7.1 and 7.4, in failure to provide information and substantiation for a claim.

RESPONSE

SmithKline Beecham said that it defined "late" treatment as being "intervention at the papule and vesicle stages". This definition was modified when referring to clinical trial data, as the late treatment group included a small number of patients with crusts and it would be misleading to imply that the data referred to patients at the papule and vesicle stages only.

Glaxo Wellcome had stated that it had requested this information from SmithKline Beecham on several occasions without success. In actual fact, the initial correspondence from Glaxo Wellcome did not clearly state that this was the information required. SmithKline Beecham had been asked once (14 August) for 'demographic' data for each treatment group in response to which it supplied the data it had (23 August). It was not clear from the requesting letter that the information required actually related to the number of patients within each lesion group. In the subsequent letter received from Glaxo Wellcome (6 September) the number of patients at each lesion stage was clearly requested but not for each treatment group. SmithKline Beecham acknowledged that the number of patients at each lesion stage in both the treatment and placebo groups were requested in a further letter from Glaxo Wellcome (31 October). However, due to the confusing nature of the previous correspondence, this was interpreted as a general request for the number of patients at each lesion stage, and not the numbers for each treatment group. As could be seen from the data there was no bias for the placebo group as implied in the letter from Glaxo Wellcome.

PANEL RULING

In the Panel's view SmithKline Beecham should have supplied the details regarding how many patients began treatment at each of the lesion stages in order to substantiate the claim in question. The Panel considered that Glaxo Wellcome had asked SmithKline Beecham for the information and this had not been provided. The Panel therefore ruled a breach of Clause 7.4 of the Code.

4 Definitions of "early" and "late" treatment

COMPLAINT

Glaxo Wellcome said that as described in point 1, during the natural history of a cold sore the progression from prodrome to vesicle usually took place quite quickly, the most distinct phase being the vesicle. It was therefore highly questionable that the *papule* should be described as a "late" stage of the cold sore, particularly in the context of normal clinical practice, where late treatment was usually understood to mean treatment initiated some considerable time after onset of an infection. The definitions of "early" and "late" as used by SmithKline Beecham were not widely recognised or accepted by the medical community; they were merely terms taken from the Vectavir clinical trial protocol. Glaxo Wellcome therefore alleged that the definitions of "early" and "late" treatment were misleading, in breach of Clause 7.2.

RESPONSE

SmithKline Beecham said that as stated in point 1, the definitions of "early" and "late" used in the Vectavir Cold Sore Cream promotional material had been previously used by Professor Spruance, including in an oral aciclovir study in which the "late" stage of a cold sore was defined as being the papule stage. SmithKline Beecham believed that this definition was a clinically meaningful one in the context of the natural history of this condition, and noted that it was before Vectavir Cold Sore Cream was launched.

PANEL RULING

The Panel considered that the allegation was similar to that in point 1 above. The Panel considered that it was doubtful whether the average doctor would consider that the papule stage should be described as a "late" stage of a cold sore. Late was more likely to be considered the crust stage. The claim was misleading and ruled to be in breach of Clause 7.2 of the Code.

5 Vectavir product licence

COMPLAINT

Glaxo Wellcome said that the Vectavir summary of

product characteristics (SPC) stated that "treatment should be started as early as possible after the first sign of an infection". There was no mention in the SPC that treatment might be delayed until the ulcer or crust stage. Glaxo Wellcome therefore alleged that the claim in question also represented a breach of Clause 3.2 in not being consistent with the SPC.

RESPONSE

SmithKline Beecham said that this allegation was unfounded. The SPC statement, "treatment should be started as early as possible after the first sign of an infection", recommended treatment as early as possible, regardless of the stage of the cold sore, ie, even patients who had reached the vesicle stage should treat as early as possible.

PANEL RULING

The Panel did not consider that the claim went outside the scope of the SPC. The SPC stated that "treatment should be started as early as possible after the first sign of infection". This was not inconsistent with what was said in the promotional material. No breach of the Code was ruled.

B Graph comparing intracellular half lives of aciclovir and penciclovir triphosphates

This appeared in the representative detail aid. Aciclovir was the active ingredient of Zovirax (Glaxo Wellcome's product) and penciclovir the active ingredient of Vectavir.

COMPLAINT

Glaxo Wellcome said that on page 3 of the detail aid was a graph which showed the longer intracellular half life of penciclovir triphosphate, compared to that of aciclovir triphosphate.

This was a misleading and unfair comparison, in breach of Clause 7.2 of the Code. The intracellular half-life was by no means the only parameter affecting the efficacy of an antiviral. For example, the affinity of the triphosphate for the viral DNA polymerase was a very important parameter of efficacy; this was 100 times greater for aciclovir triphosphate compared with penciclovir triphosphate, but this had not been mentioned. To show a comparison of the intracellular half lives in isolation of other factors was completely meaningless.

Glaxo Wellcome referred to Case AUTH/277/3/95 in which Wellcome was ruled in breach of Clause 7.2 for presenting data on the superior DNA polymerase affinity of aciclovir triphosphate without counterbalancing it by referring to the greater intracellular concentration of penciclovir triphosphate.

RESPONSE

SmithKline Beecham said that Glaxo Wellcome stated that the affinity of aciclovir triphosphate was approximately 100 times greater than that of penciclovir triphosphate and had referred to a case in which SmithKline Beecham complained about the use of a graph by Wellcome in which the approximate 100 fold difference in affinity for DNA polymerase between aciclovir and penciclovir was shown, but which took no account of the approximately 100 fold greater affinity of viral thymidine kinase for, and the intracellular concentration of, penciclovir. The intracellular concentration of a drug was different to the intracellular half-life.

The long intracellular half life of penciclovir triphosphate was an important parameter as this highlighted the long period for which the active antiviral agent was present in the virally infected cell and so able to exert its antiviral effect.

PANEL RULING

The Panel accepted SmithKline Beecham's view that the long intracellular half-life of penciclovir triphosphate was an important parameter in this area. Nonetheless, the Panel considered that failure to balance the claim in this respect with a reference to the fact that the affinity of the triphosphate for the viral DNA polymerase was 100 times greater for aciclovir triphosphate than for penciclovir triphosphate was misleading and a breach of Clause 7.2 was ruled.

C Patient assessed data

This allegation and those in D and E below related to a double page spread at pages 4 and 5 in the representative detail aid with the overall heading "Clinically effective - with early or late treatment". The left hand page referred to results with Vectavir (allegations C & D). The right hand page referred to results with aciclovir (allegation E)

COMPLAINT

Glaxo Wellcome said that the data presented for time to loss of classical lesions and time to loss of lesion pain were patient assessed data. It was not clear why physician assessed data had not been shown, when, according to the study protocol, patients were "seen in the clinics within 24 hours of initiating therapy and at frequent intervals thereafter to assess lesions, pain, viral shedding and adverse reactions". It was possible that the physician assessed data were not statistically significant and, if this was the case, this should be pointed out in the promotional material.

RESPONSE

SmithKline Beecham said that it chose to use patient assessed data to support the promotional claims for Vectavir Cold Sore Cream as assessments were more frequent than clinic visits and, therefore, gave a more accurate estimate of the true clinical benefit derived from applying Vectavir Cold Sore Cream. However, the physician assessed data were also highly statistically significant and were closely correlated with the patient assessed data (correlation coefficients ranged from 0.74 to 0.93). Glaxo Wellcome had never requested this data from SmithKline Beecham.

PANEL RULING

The Panel noted that the material indicated whether the

data was patient or investigator assessed data. The Panel could see no reason why patient assessed data should not be given in relation to the treatment of cold sores. There was a subjective element in the condition. Clearly use of patient assessed data might be misleading if physician assessed data gave a different picture but this was not the case here. The Panel ruled that there was no breach of the Code.

D Statistical versus clinical significance of patient assessed data

COMPLAINT

Glaxo Wellcome said that also not mentioned in any of the promotional items was the fact that these data represented a clinical advantage to the patient of only 0.8 and 0.7 days respectively, compared to placebo. This suggested that, although the results were statistically significant, they might not be perceived as clinically significant by the medical community.

Glaxo Wellcome therefore alleged that these data had been presented in a misleading way, in breach of Clause 7.2.

RESPONSE

SmithKline Beecham said that the clinical benefit obtained from treatment with Vectavir Cold Sore Cream in terms of approximately a one-day reduction in the median time to healing was compared with a vehicle placebo and was comparable with that reported in studies of aciclovir cream. Furthermore, the clinical benefits should be considered in context of the usual duration of untreated episodes (no vehicle placebo) which was approximately 8-10 days compared with that of Vectavir Cold Sore Cream which was approximately 5-6 days. As patients with herpes labialis could experience more than four cold sore episodes per year (Consumer Quantitative Research for Vectavir Cold Sore Cream) and as cold sores could have a profound effect on the confidence and psychosocial behaviour of patients, the cumulative benefit of Vectavir Cold Sore Cream treatment of 1-2 weeks per year was surely clinically relevant.

RULING

The Panel noted that the comparison was between Vectavir Cold Sore Cream and a vehicle placebo. The Panel considered that, although the time difference was relatively small, it would nonetheless be enough to be of significance to patients and ruled that there had been no breach of the Code.

E "Results with aciclovir cream Early treatment"

COMPLAINT

Glaxo Wellcome referred to a table of results from four Zovirax cream studies which it alleged was misleading, in breach of Clause 7.2.

The table in question listed four studies with the number of patients evaluated in each. The table indicated by the use of ticks and crosses whether resolution of lesions and reduction of pain had been found to be significant or not significant in each study. The table also indicated that none of the studies had looked at the reduction in viral shedding.

The table was subheaded "Early treatment", further emphasising the misleading notion that Zovirax treatment must begin early in order to have an effect, whereas Vectavir treatment could work even if delayed. In fact, as pointed out previously, patients began treatment within one hour in the Vectavir studies, whereas the Zovirax cream studies allowed treatment to begin up to 12 or even 24 hours after the onset of symptoms (more closely reflecting actual clinical usage). Furthermore, some of the patients in the Zovirax cream trials had papules or vesicles on entry which, if categorised using the SmithKline Beecham definition, would constitute late treatment with Zovirax. It should also be pointed out that one of the four Zovirax cream studies in the table (Raborn *et al*) used the "Mark III" cream formulation, which did not contain sodium lauryl sulphate (a skin penetration enhancer). It was therefore inappropriate to include this with the other three studies in an efficacy tabulation.

The studies of Zovirax cream were not designed specifically to demonstrate reduction of pain or reduction of lesion size/severity and did not attempt to determine viral shedding. It was therefore not valid to compare these with the Vectavir trials, which had different end points. SmithKline Beecham's definitions of "early" and "late" were very subjective (as explained above), and comparisons should not be made across clinical trials. Furthermore, no mention had been made of the fact that treatment during the prodrome stage with Zovirax cream had been shown to prevent the lesion appearing in a proportion of patients, whereas the large Vectavir meta-analysis had failed to demonstrate this important clinical benefit. It was therefore misleading to compare the Zovirax and Vectavir studies in breach of Clause 7.2.

RESPONSE

SmithKline Beecham said that it had reviewed the table in question and accepted that as the study by Shaw *et al* did indeed include patients that were at the papule or vesicle stage, this was a breach of Clause 7.2 of the Code and the term "early treatment" should be removed. With this amendment, however, the data in the table were valid. The study by Raborn *et al* did not make it clear that the formulation of the product used was different to that used in other studies. In addition, Vectavir Cold Sore Cream also did not contain sodium lauryl sulphate. These were the only topical aciclovir cream 5% studies that SmithKline Beecham were aware of from published literature and it was useful to include the data in the detail aid.

RULING

The Panel considered that the implication of the table was that treatment with aciclovir needed to be started early whereas treatment with Vectavir did not. The Panel noted that SmithKline Beecham had accepted that the words "early treatment" should be removed. A breach of Clause 7.2 was ruled.

SmithKline Beecham had not known of the formulation

difference but this now needed to be taken into account in future promotional material.

F "Significantly less irritant than aciclovir cream"

This claim appeared at page 6 in the representative detail aid on a double page spread under the overall heading "Well tolerated therapy - and a significant price advantage".

COMPLAINT

Glaxo Wellcome said that the study referred to (Lavender *et al*) used Zovirax cream at an unlicensed dosage regimen and it tested the products under conditions of "occlusion" which did not represent normal clinical usage. Furthermore, the conclusions were based on only 19 subjects. This did not take into account the enormous amount of clinical experience with Zovirax cream since it was licensed in 1983, during which time it had demonstrated an extremely good safety profile, and received a licence for over the counter (OTC) sale in many countries worldwide. This was an unfair comparison, in breach of Clause 7.2.

RESPONSE

SmithKline Beecham said that the Vectavir Cold Sore Cream and aciclovir cream 5% irritancy study it had conducted was a valid comparative study conducted to regulatory guidelines for evaluation of relative dermal irritancy between different topical formulations. Furthermore, the data sheet for aciclovir cream 5% mentioned that erythema and itching had been reported as side effects in a small proportion of patients.

PANEL RULING

The Panel did not consider that the claim had been adequately substantiated. The study had used occluded application to the backs of volunteers and this was not considered to be an adequate basis for the support of the claim. The SPC for Vectavir said that it was only for use on the lips and around the mouth. It was ruled there had been a breach of Clause 7.2.

PRESS MATERIALS DATED 4 JUNE 1996

G "Setting a new standard in the management of herpes labialis"

This statement was used as the heading to the press release and on each of the documents making up the press materials. These being a programme, a news release, speakers' biographies and four medical press backgrounders, one on Vectavir, one on herpes labialis, one on sufferers' and general practitioners' perspectives and one on SmithKline Beecham.

COMPLAINT

Glaxo Wellcome said that this statement was misleading on a number of counts; no difference in standards had been demonstrated, particularly as there was no comparative study with established treatments.

i) It implied improved efficacy compared with existing antiviral agents, when in fact Vectavir was compared only with placebo.

ii) It was based on the misleading premise that Vectavir was effective when used as a delayed or "late" therapy - up to and including the crust stage of a cold sore.

iii) Large clinical studies had failed to demonstrate the ability of Vectavir to prevent lesion formation, an important benefit which had been demonstrated for Zovirax cream. This was despite the fact that over 90% of the patients in the Vectavir trials experienced a prodrome either "always" or "most of the time", and all the patients were instructed to self-initiate treatment within one hour of noticing the onset of a cold sore, thereby maximising the chances of demonstrating a lesion prevention effect.

iv) Vectavir had to be applied every two hours, compared to every four hours for Zovirax cream.

Glaxo Wellcome therefore considered this statement to be misleading and in breach of Clause 7.2, as there was no evidence whatsoever to show that Vectavir was setting a new standard in cold sore treatment.

RESPONSE

SmithKline Beecham said that it had at no time claimed that Vectavir Cold Sore Cream was better than aciclovir cream 5% or any other topical antiviral agent. Such a claim would require a head-to-head study of Vectavir Cold Sore Cream and the other topical antiviral in question. To date, such a study had not been conducted.

In the press release for Vectavir Cold Sore Cream, it was stated that "Vectavir, penciclovir, 1% cream has been shown in the largest clinical trial of topical antivirals undertaken to date, to significantly reduce the time to loss of lesions and loss of lesion pain, Vectavir is the first topical antiviral to show clinical benefit with both early and late treatment." SmithKline Beecham believed this statement to be correct.

The statement, "Setting a new standard", did, however, highlight the fact that there was greater consistency in the clinical data with Vectavir Cold Sore Cream compared with aciclovir cream 5% and other topical treatments for herpes labialis. In addition, the clinical trials for Vectavir Cold Sore Cream were robust involving over 3,000 patients, compared with 175 patients in the published aciclovir 5% studies, and included controlled data for several clinically relevant stages of a cold sore.

Although the clinical studies with Vectavir Cold Sore Cream did not show an effect on the prevention of herpes labialis lesions, this was probably due to the fact that patients with frequent "false" prodromes or a tendency for their episodes to abort spontaneously were excluded from the clinical studies. Twenty-five per cent of cold sores aborted spontaneously. Although Glaxo Wellcome claimed that aciclovir cream 5% was capable of aborting herpes labialis lesions, as far as SmithKline Beecham was aware, this claim was based on data from only one small study [n=49].

The total number of doses applied during a typical treatment course with Vectavir Cold Sore Cream was similar to that with aciclovir cream 5%, namely 24

applications for Vectavir Cold Sore Cream (six times per day for four days) and 25 applications for aciclovir cream 5% (five times a day for five days).

RULING

The Panel considered that the statement "Setting a new standard in the management of herpes labialis" was too strong for use in a press release which would be going to the lay press. The implication was that Vectavir was an improvement on other products used to manage herpes labialis. To date no study directly comparing Vectavir and other topical antivirals had been conducted. The statement was not balanced and it was ruled that there had been a breach of Clause 20.2 of the Code.

H "...by the time patients get to them it is too late to treat with existing topical antiviral agents"

This statement appeared in the news release.

COMPLAINT

Glaxo Wellcome said that this statement implied that the product licence for Vectavir cream was significantly different from that for Zovirax cream with respect to initiation of therapy (as described earlier). Glaxo Wellcome therefore considered this statement to be misleading and in breach of Clause 7.2.

RESPONSE

SmithKline Beecham said that this was a statement made by Dr Michael Lewis, a Senior Lecturer and Honorary Consultant in Oral Medicine at the University of Wales College of Medicine, and reflected his personal experience of the herpes labialis field and where he considered other topical antivirals to be currently effective.

The statement was also supported by data from a study of 100 UK general practitioners (The GP's perspective on cold sores) conducted on behalf of SmithKline Beecham. In this survey, 77% of GPs felt unable to offer antiviral therapy to herpes labialis patients who presented late as available therapy needed to be applied early.

PANEL RULING

The Panel considered this allegation was similar to point 1 of A above. There was again the implication that Vectavir could be used on patients presenting late, including those at the crust stage. The period during which the product was effective needed to be better defined. A breach of Clause 7.2 was ruled.

I Promotion of Vectavir to the lay press

COMPLAINT

Glaxo Wellcome said that following the UK launch of Vectavir on 4 June 1996, the product received considerable coverage not only in the medical press, but also in a number of publications directed towards the general public.

For example, the Radio Times 3-9 August 1996, carried a highly misleading article about Vectavir cream, stating that the product "goes one step further" than existing agents. The Daily Mail, 5 June 1996, featured an article subtitled "NHS pioneers powerful new remedy that should ease cold sore misery for millions". This article even mentioned the trade name of the product, the generic name, and the indication.

Whilst the press information kit was clearly labelled "For the attention of the accredited medical correspondent only", Glaxo Wellcome was aware that a freelance journalist requesting information for an article on cold sores for a women's magazine was provided with this same press kit. This clearly indicated that the material was not circulated only to accredited medical correspondents. Further evidence that it was SmithKline Beecham's intention to promote Vectavir to the public could be found in a recent article in "Pharmaceutical Marketing" in which the company stated that "the UK has presented its own set of problems to be overcome. Not least is the ban on direct consumer advertising, although successful PR resulted in wide press coverage of Vectavir".

Glaxo Wellcome alleged that this constituted the advertising of a prescription-only medicine to the general public, in breach of Clause 20.1 of the Code. Furthermore, mention of the availability of this product from doctors via the NHS represented a breach of Clause 20.2 of the Code and there was further breach of this clause in the non-factual and unbalanced nature of the information.

RESPONSE

SmithKline Beecham said that it always did the utmost to ensure that any press materials associated with a product launch were distributed appropriately. In the case of Vectavir Cold Sore Cream, only accredited medical correspondents and a correspondent from the Financial Times were invited to the product launch. SmithKline Beecham had no right of veto on the final articles that were used by the media. Whilst not condoning the use of such materials in this way, SmithKline could not accept responsibility if a freelance medical correspondent independently used the material from this launch in articles for inclusion in non-medical journals.

PANEL RULING

The Panel noted that while at one time the Code had referred to the need to supply information about prescription medicines to accredited medical correspondents only, there was no such requirement in the current Code and there was no reason why appropriate material should not be sent to the press generally, provided that the requirements of Clause 20 were met.

The Panel did not consider that there had been a breach of Clause 20.1 of the Code as the circumstances did not amount to the advertising of a prescription only medicine to the general public. The general question of over emphasis had already been dealt with. Articles appearing in the media were judged not upon their content but upon what the company concerned, or its agents, had supplied.

Complaint received **17 December 1996**

Case completed **12 March 1997**

CASE AUTH/484/12/96

NAPP v SANOFI WINTHROP

Promotion of Morcap SR

Napp Laboratories complained about seven promotional items for Morcap SR issued by Sanofi Winthrop all of which contained comparisons of the product with modified release morphine sulphate tablets.

The Panel did not accept that the use of the abbreviations "MRMST" or "MR MST" to mean modified release morphine sulphate tablets was tantamount to using Napp's brand name MST Continus, and ruled no breach of the Code.

The Panel did not consider that claims relating to the pharmacokinetics of Morcap SR were unbalanced or misleading or used in such a way as to imply a clinical benefit for Morcap SR. No breach of the Code was ruled. A graph in a GP mailing was considered to have accurately reflected the pharmacokinetic profile of both Morcap SR and a modified release morphine sulphate tablet and so was not in breach of the Code.

A claim in the technical brochure relating to the sustained released profile of Morcap SR compared to that of modified release morphine sulphate tablets was considered ambiguous and ruled in breach of the Code. The Panel did not, however, consider the claim disparaging of the competitor product and ruled no breach in that regard. A claim relating only to the sustained release profile of Morcap SR was one of fact and did not imply any efficacy or clinical benefit for the product. No breach was ruled.

The Panel did not consider that patient global assessment data had been presented in an unbalanced or misleading way and ruled no breach of the Code.

A claim in the technical brochure comparing the efficacy of Morcap SR with that of modified release morphine sulphate tablets was not inaccurate as alleged and no breach of the Code was ruled. A leavepiece which set out how to start patients on Morcap SR, or transfer then from other morphine regimens, had the headline "straightforward to use". The Panel did not consider that this heading implied an exact equivalent of Morcap for every dose of oral morphine a patient could be taking. A once daily dosage form could be viewed by either the patient or the doctor as straightforward to use and no breach was ruled.

The Panel considered that a claim in the technical brochure which linked the absorption profile of Morcap SR to a potential for less morphine-related side effects compared to modified release morphine sulphate tablets was ambiguous and did not reflect clinical experience. A breach of the Code was ruled.

Napp Laboratories Limited complained about the promotion of Morcap SR by Sanofi Winthrop Limited. The promotional items at issue were:

1 Journal advertisement

2 Technical brochure

3 "Dear Doctor" letter sent to all GPs

4 "Dear Nurse" letter sent to Macmillan/cancer nurses

5 GP mailer sent to GPs with an interest in cancer care

6 Conversion leavepiece summarising information about dosing of Morcap SR

7 GP magazine outsert used once only

The allegations were considered as follows.

A Use of terms "MRMST" and "MR MST" to identify MST Continus tablets

This allegations referred to the journal advertisement, the technical brochure, the GP mailer, the conversion leavepiece and the outsert.

COMPLAINT

Napp pointed out that "MRMST" was defined by Sanofi Winthrop as meaning "modified release morphine sulphate tablet". There was no definition in the technical brochure of "MR MST".

Napp alleged that the descriptions "MRMST" and "MR MST" were obviously similar to its MST brand name in spite of Sanofi Winthrop's attempt to use them as generic abbreviations, readers would clearly understand them as references to the Napp product. A breach of Clause 7.10 was alleged.

"MST" was a registered trade mark with Napp Laboratories being the registered user. Napp acknowledged that the full product name was "MST Continus" but the "MST" mark was used on its own and was well recognised by health professionals. It was not a generic abbreviation for morphine sulphate tablets. It was distinctive of Napp's products and used for its controlled release suspensions as well as for tablets.

Wherever the expressions "MRMST" were used they referred to Napp's MST Continus tablets, as all of the relevant references were to trials using MST Continus tablets or an equivalent product. Napp had not consented to the use of the MST brand name by Sanofi Winthrop. It appeared that Sanofi Winthrop had attempted to find a way to use the MST brand name without breaching Clause 7.10 of the Code but in a way which doctors would still identify as a reference to Napp's product as the market leader.

RESPONSE

Sanofi Winthrop submitted that neither "MRMST" nor "MR MST" were, or ever had been, a brand name. The initials, which were qualified clearly with every use in the promotional material were accurately descriptive of a modified release morphine sulphate tablet. Similar initials were widely used in medicine to refer to drugs or classes of medicines eg NSAIDs (non-steroidal anti-inflammatory drugs), ACEIs (angiotensin converting enzyme inhibitors), and could not be claimed exclusively by any one product.

In normal commercial use the twice daily controlled release morphine sulphate product promoted by Napp was marketed under the brand name "MST Continus".

This was how it appeared in MIMS and other reference publications. Indeed the British National Formulary stated that "prescriptions must be written "MST Continus tablets"".

Sanofi Winthrop noted that "MST" was a registered trade mark for analgesic preparations, but denied that it had used that mark. In the promotional materials the company had used what it considered to be a sensible and convenient abbreviation for the relatively complicated expressions "Immediate Release Morphine" (IRM) and "Modified Release Morphine Sulphate Tablets" (MRMST). Napp did not, and could not, have any form of priority monopoly. In each of the materials where the abbreviation was used there was clear reference to its full meaning.

PANEL RULING

The Panel noted that the brand name of Napp's product was "MST Continus". Sanofi Winthrop had used the descriptions "MRMST" and "MR MST". The Panel did not accept that Sanofi Winthrop had used Napp's brand name and therefore no breach of Clause 7.10 was ruled. The question of whether Napp's intellectual property rights had been infringed was not one for the Panel to consider.

B Claims that Morcap SR had a superior pharmacokinetic profile and superior sustained release profile compared to MST Continus tablets

This allegation referred to all seven of the promotional items.

COMPLAINT

Napp alleged that Sanofi Winthrop repeatedly claimed that Morcap SR had a superior pharmacokinetic profile and a superior sustained release profile to MST Continus tablets. This was presented as a key promotional point in such a way as to imply some clinical advantage which was not substantiated by the literature presented. This was alleged to be misleading and not capable of substantiation in breach of Clauses 7.2 and 7.3.

The technical brochure on page 17 stated that "...Morcap SR displayed a superior sustained-release steady state pharmacokinetic profile based on the following parameters: higher Cmin, longer Tmax, and less fluctuation in plasma morphine concentration throughout the dosing interval (despite having a dosing interval double that of MRMST). In addition, Morcap SR displayed a longer duration of plasma morphine concentration equal to or exceeding 75% Cmax further reflecting the superior sustained-release profile of Morcap SR as compared to MRMST."

On page 15, the technical brochure stated that "...Morcap SR showed a slower absorption rate (time to peak concentration, longer T_{max} 8.6 versus 2.5h) and a longer duration above 75% of peak concentration (6.3 hours compared to 2.5 hours) than MRMST, indicating the superior, sustained-release characteristics of Morcap SR."

The "Dear Doctor" and "Dear Nurse" letters stated that Morcap's novel sustained-release mechanism ensured a superior pharmacokinetic profile in comparison to a currently available 12 hourly modified-release product.

The conversion leavepiece stated that once daily Morcap SR had a "Sustained-release profile superior to a MRMST".

The journal advertisement, the GP mailer and the outsert made claims that Morcap SR had less fluctuation in blood [plasma] morphine levels compared to a "MRMST".

Napp also made the following additional comments.

1 Napp pointed out that the difference in fluctuation in plasma morphine levels between Morcap SR and MST Continus tablets described in the technical brochure (page 17) was very small. On examining the plasma profile graph the trough concentrations (Cmin) for each product, reported to be significantly different, appeared virtually identical. The numerical data reflected the same picture. Even though the difference in fluctuation was reported to be statistically significant ($P<0.05$ ANOVA), the effects of the difference between 1.4 ± 0.4 and 1.6 ± 0.5 were so small that it would be very unlikely to be clinically perceptible or relevant.

2 The most straightforward calculation of the difference in fluctuation would be Cmax ÷ Cmin. However, the referenced study (Gourlay, 1995) calculated the difference in fluctation by way of Cmax - Cmin ÷ average concentration. The comparison was made between Morcap SR 24 hourly and MST Continus tablets 12 hourly. The area under the concentration curve (AUC) for Morcap SR 24 hourly was 10% higher than that for MST Continus tablets 12 hourly. This was not a statistically significant difference and, as Sanofi Winthrop admitted, the availability of morphine to the patient was not affected by this difference. However, the AUC formed the basis of the calculation of average concentration which, in turn, formed part of Sanofi Winthrop's calculation of the difference in plasma morphine level fluctuation between the two products. The results of this was that the 10% difference in AUC contributed the major part of the 14% difference in the fluctuation of the plasma morphine levels. Sanofi Winthrop, therefore, had used the formula which produced the most favourable result for its purpose.

3 It was not proven that the pharmacokinetic profile of Morcap SR 24 hourly was superior to, rather than just different from, the profile for MST Continus tablets 12 hourly. In the technical brochure (page 9) Sanofi Winthrop claimed that the aim of any sustained release morphine preparation was to provide even plasma levels for the entire dosing interval. It was notable that whilst Morcap SR 12 hourly had a relatively flat profile, Morcap SR 24 hourly did not.

What Sanofi Winthrop did not point out was that the efficacy of opioid analgesics, such as morphine, was at least in part a function of the rate at which the medicine achieved therapeutic concentration at opiate receptors. A long standing case in point was the use of lower doses of intravenous as compared to intramuscular morphine. In both cases, the same amount of morphine attained access to the systemic circulation but the faster rate achieved with intravenous injections provided greater efficacy than that attained with intramuscular morphine. Similarly, the same administered milligram dosages of different oral controlled release morphine formulations had been shown to achieve different degrees of analgesia

depending on the rate at which morphine was released and absorbed into the systemic circulation for interaction with opiate receptors (Bloomfield 1993 and Cooper 1994).

Sanofi Winthrop's emphasis on pharmacokinetic superiority was therefore misleading as the company had been selective in the choice of criteria.

4 It was important to note that in the various clinical trials which Sanofi Winthrop carried out comparing Morcap SR to MST Continus tablets no significant difference had been established between the products in terms either of clinical efficacy or side effects. Notwithstanding this, the Sanofi promotional literature used the claim of superiority in such a way as to imply some clinical benefit. In the "Dear Doctor" and "Dear Nurse" letters Sanofi Winthrop claimed that the superior pharmacokinetic profile of Morcap SR 24 hourly "... allows once daily dosing..... which more patients rated "good" or "very good". In other words, Sanofi Winthrop was saying that the "superior pharmacokinetic profile" caused more patients to rate its product more highly.

In addition, it was noticeable in the conversion leavepiece that the first of only five bullet points about Morcap SR was that it had a "sustained release profile superior to a MRMST". In the absence of qualification, the implication was that Morcap SR worked better and would therefore be more effective in treating a patient's pain. Again, this was contrary to Sanofi Winthrop's clinical evidence.

5 Whilst Sanofi Winthrop had failed to show any clinical benefit for its product, either 12 hourly or 24 hourly, over MST Continus tablets, a recent study conducted in New Zealand had shown that MST Continus tablets were significantly more effective than Morcap SR in all measures of both maximum and total analgesic effects (Brown *et al* 1996). The study was a single dose, randomised, double-blind, parallel group comparison of the analgesic efficacy to the two products in 100 patients with moderate or severe pain. The degree of the difference in efficacy was that which had usually been associated with an approximate two-fold difference in morphine dosage. The study utilised a post-operative pain model and a 60mg dose of the oral morphine formulations. The post-operative pain model had been well established for many years as a sensitive measure for determining the relative efficacy of analgesics in general, regardless of the patient population in whom the drug was intended for general use (Max *et al* 1991).

It was also worth noting that the results of the Toner clinical study reported in the technical brochure (page 20), which compared Morcap SR 12 hourly and immediate release morphine sulphate solution, although not statistically significant suggested that the immediate release solution was slightly better in treating pain than the Morcap SR. The study was small with only 24 patients and it was not unreasonable to anticipate that had the study involved more patients, it might have had sufficient power to detect clinically relevant statisitical differences between the two treatments. It was also notable that this study adopted a crossover design.

6 In summary, the difference in fluctuation between the two products was exaggerated by the method of calculation. Even so the difference was so small that it would be unlikely to have any clinical effect. No clinical effect had been proven and, moreover, there was evidence to suggest that MST Continus tablets were more effective than Morcap SR. There was no justification for the unqualified promotional claims made by Sanofi Winthrop regarding the superiority of its product.

RESPONSE

Sanofi Winthrop submitted that there was sound clinical pharmacology data which supported the claim that Morcap SR did indeed have an advantage in a wide range of pharmacokinetic parameters and as a sustained release product, could therefore be said to have "a superior pharmacokinetic profile". Any claims concerning clinical advantage were restricted to where they could be substantiated by both general clinical pharmacology and, where appropriate, well controlled clinical trials, and not based solely on pharmacokinetic data.

Where superior profile was claimed it was always in the context of a superior pharmacokinetic or sustained release profile. The pharmacokinetic/sustained release profile was important in terms of a once daily product to provide for 24 hour efficacy without an increase in side effects over more frequent dosing. The claim was not presented at any time to imply clinical benefit, eg in the "Dear Doctor" and "Dear Nurse" letters the pharmacokinetic statement was not highlighted and was immediately followed by a statement that the result of this superior pharmacokinetic profile was a once daily licence, but with comparable efficacy and tolerability.

It was important that doctors understood that it was the improved pharmacokinetic parameters that enabled a product which could be given twice daily to also be given once daily (as in Morcap SR's licence, compared with MST Continus which was only licensed for twice daily administration). The flexibility in the licensed use was dependent solely on the improved pharmacokinetic profile.

Morcap SR was a sustained release morphine preparation which was licensed for the prolonged relief of chronic, moderate to severe pain. A sustained release product was judged by its ability to provide an even drug plasma level during the entire dosing interval compared to conventional release preparations.

Morcap SR capsules provided a novel form of morphine release. The capsule consists of polymer coated pellets of morphine sulphate contained within a gelatine capsule. After oral administration the gelatine capsule dissolved in the stomach to release the polymer coated pellets. The pellets had pH dependent drug release profile. In the stomach where the pH was low the morphine was not released. However, as the pellets passed through the pyloric sphincter into the less acidic small intestine, morphine was slowly released in a sustained manner. Minute pores developed in the polymer coat of the pellets through which the morphine was released by passive diffusion so that the release occurred over several hours in the small intestine. It was this mechanism that provided the sustained release profile of Morcap SR.

The relief of chronic pain, particularly relating to cancer, was an area where sustained release preparations had

advantages in some patients. These advantages included the reduction in the dosing frequency, the provision of a more even plasma level of the analgesic, thereby reducing the possibility of symptom breakthrough caused by trough drug plasma concentrations. They may also potentially be associated with fewer of the adverse effects caused by high peak drug plasma concentration. Extracts from textbooks of clinical pharmacology were provided to support the submission.

Sanofi Winthrop alleged that when comparing different sustained release preparations, the important pharmacokinetic indicators were :-

Cmax - the maximum plasma concentration during an observation period

Tmax - the time at which the maximum of plasma concentration Cmax was reached

AUC (area under the curve) - a guide to the total absorption of the drug

Cmin - the minimum concentration during steady state dosing

"Fluctuation" - the variation between peak and trough plasma concentration.

Time during the observation period when the plasma concentration was greater than, or equal to, a certain % of the Cmax, eg 75% as used by Gourlay (a mark for the extent of control of sustained release).

There was sound clinical data which supported the claim that Morcap SR did have an advantage in these parameters and, as a sustained release product, could therefore be said to have "a superior pharmacokinetic profile".

Gourlay G K (1995) completed a randomised, double-blind, placebo controlled, double-dummy, crossover study of once daily Morcap compared with 12 hourly MST Continus in 24 patients with moderate to severe cancer pain. The results of this study were presented in the technical brochure along with all the pharmacokinetic data which was regarded as necessary to compare sustained release preparations.

For completeness and accurately to represent the data, two ways of presenting the data were provided for the reader. The mean plasma concentrations at each time point were represented in a graph, while the overall values for the different parameters were represented in a table.

The claim that Morcap SR, as a sustained release product, had a superior pharmacokinetic profile compared with MST Continus was based on the fact that in comparison to MST Continus, in each of the following pharmacokinetic parameters, Morcap SR had a statistically significant advantage.

T_{max} was significantly longer with Morcap SR (10.3hrs vs 4.4hrs)

The minimum concentration of morphine in the steady state was significantly higher for Morcap SR (9.9mg/ml vs 7.6mg/ml)

The time greater than or equal to 75% of C_{max} was significantly greater for Morcap SR (6.0hrs vs 4.8hrs)

The fluctuation was significantly less for Morcap SR (1.4 vs 1.6)

All these differences were statistically significant with p values of <0.05.

Sanofi Winthrop commented as follows on the additional points raised by Napp.

1 The differences between the graph and the table were discussed above. The difference in the fluctuation was just one of the parameters used to compare the two pharmacokinetic profiles. Claims of the smoother profile of Morcap SR compared with MST Continus were based on the overall picture including the fact that fluctuation in plasma concentration was less for Morcap SR compared with MST Continus.

2 Concerning estimation of the fluctutation in plasma levels described in the pharmacokinetic section of the technical brochure (page 17), Gourlay used the equation (Cmax - Cmin) ÷ average concentration, to assess the fluctuation of each profile. This had the advantage of allowing for differences in the total drug absorption and provided a more accurate reflection of underlying variation in plasma levels than if the area under the curve was not taken into account. For example, if the average concentration of a drug was 10mg per litre and there was a difference between maximum and minimum concentrations of 5mg per litre this would be a lot more significant than if there was a difference between Cmax and Cmin of 5mg with the average concentration of 100mg per ml. In less extreme examples (as in this case, where the difference in area under the curve was approximately 10%) these differences still needed to be taken into account.

The equation suggested by Napp to measure fluctuation, namely, Cmax ÷ Cmin, was less able to take into account variations in area under the curve. However, even if the equation suggested by Napp was used on the data from the Gourlay study the fluctuation (Cmax ÷ Cmin) for Morcap SR (3.77) was still less than for MST Continus (4.85).

Sanofi Winthrop submitted that Gourlay was correct in using the equation (Cmax - Cmin) ÷ average concentration as a robust measure of fluctuation and that no attempt was made to distort the figures as the same comparative result was obtained using Napp's suggested method of calculation (Cmax ÷ Cmin).

3 Sanofi Winthrop submitted that the preferred pharmacokinetic profile for the adequate relief of acute pain from a single dose of morphine in the post-operative period, was different from that required for the prolonged use of morphine for the relief of chronic, moderate to severe pain. The licence for Morcap SR was for the prolonged relief of chronic, moderate to severe pain. It was not licensed for single dose administration for the relief of acute or post-operative pain.

The two studies used by Napp to support its assertions, where there was requirement for a single dose to achieve rapid pain relief, were not relevant to the promotion of Morcap SR as they were outside the licence.

Additionally, the two studies did not use Morcap SR as a comparator to MST Continus. The first, by Bloomfield *et al*, compared MST Continus with Oramorph SR (a product marketed by Boehringer Ingelheim in the UK) in patients undergoing Caesarean section or abdominal hysterectomy. This was a single dose study with the one dose being given on the 2nd or 3rd post-operative day. The second by Cooper *et al* also compared MST Continus and Oramorph SR. Each patient group was given a single dose of morphine following one of a variety of orthopaedic operations. The fact that MST Continus appeared to provide better analgesia than a competitor product, in the circumstances of a single dose to a group of normally healthy patients with acute pain, had little relevance when discussing the provision of pain relief for moderate to severe pain for a prolonged period of time.

The sustained release mechanism of Morcap SR designed for chronic use, which achieved maximum plasma concentration of morphine after considerable delay (more than 8 hrs after adminstration in the case of Morcap SR) would not be considered a suitable pharmacokinetic profile for the relief of acute pain.

For its licensed indication the pharmacokinetic profile displayed by Morcap with its longer Tmax, less fluctuation, and greater length of time ≥ Cmax 75% was more appropriate. Sanofi Winthrop had not been selective in its choice of criteria, but merely restricted the promotional material to that relevant to the licensed indication.

4 That the pharmacokinetic profile of the sustained release Morcap SR allowed once daily dosing was reflected in the summary of product characteristics (SPC). Sanofi Winthrop maintained that with regard to pain relief and side effect profile, there was no evidence that there was a significant difference between Morcap SR and MST Continus and for this reason all the promotional material stated that Morcap SR was "as effective as a MRMST".

However, in the largest comparative study between Morcap SR and MST Continus, a randomised, double-blind, double-dummy, parallel group design study involving 172 cancer patients receiving morphine for the licensed indication of relief of chronic moderate to severe pain by Kerr *et al* 1995, there was a statistically significant difference in the patient global assessment favouring the once daily Morcap SR preparation. 89% of patients reported Morcap SR to be "good" or "very good" compared with 68% reporting the same level of satisfaction with MST Continus. Kerr noted that "... Patient global assessment of pain control scores significantly favoured the Kapanol [Morcap SR] 24 hourly group as opposed to the MS Contin group."

The promotional material for Morcap SR stated (without the editing in the complaint) that:

Morcap SR's "... novel sustained release mechanism ensures a superior pharmacokinetic profile in comparison to a currently available 12 hourly modified release product. This in turn, allows once daily dosing with comparable efficacy and tolerability, which more patients rated "good" or "very good"".

This was supported by the following features of Morcap SR:

Morcap did have a novel release mechanism

Its superior pharmacokinetic profile had been demonstrated compared to a currently available 12 hourly product (MST Continus)

Its pharmacokinetic profile allowed once daily dosing

The once daily dosing provided comparable efficacy and tolerability

More patients rated it as "good" or "very good" compared to a currently available 12 hourly modified release product

The bullet point "sustained release profile superior to MRMST" in the conversion leavepiece appeared under the headline "24 hour control of cancer pain". Health care professionals would understand the statement: "sustained release profile superior to MRMST" to mean just that, that the pharmacokinetic profile allowed dosing once every 24 hours. This was further qualified in the subsequent bullet point stating "reliable 24 hour pain control".

5 Extensive clinical trials had demonstrated that Morcap SR was as effective as other sustained release products for its licensed indication of "the prolonged relief of chronic, moderate to severe pain". This was consistently reflected in its promotional material.

The study referred to by Napp by Brown *et al*, was another single dose post-operative study where the one dose was given following one of a variety of orthopaedic operations.

Sanofi Winthrop did not accept that the reference of Max *et al* (1991), to justify some of the arguments in this complaint, was presented in a balanced way. Max contributed a chapter titled "Single Dose Analgesic Comparisons" to a book on Advances in Pain Research and Therapy. The chapter concentrated on single dose analgesia and not the relief of chronic pain. It was stated that in choosing the type of patients to be admitted to a study consideration needed to be made as to the specific question being addressed. The chapter stated:

"In the 30 years since Beecher asserted that in assessing analgesics in man, "neither source of pain nor type (acute or chronic) are important considerations" research has revealed distinctions between types of pains with different sensitivities to different analgesics".

The chapter discussed the place of using a post-operative model where a narrowly defined group was required.

"A narrowly defined patient group is particularly important when the purpose of the study is to address a particular biological principle of pain relief".

This was compared with the circumstances where there was a need for a broader range of patients and stated that

"for application to clinical practice, a conclusion based on experience with a broad range of patients may be more convincing than one based on a single sub-set of patients".

While Max did regard the post operative pain model as well established, it was very much in the context of a "single dose analgesic comparison" in a narrowly defined patient group. Sanofi Winthrop did not therefore think that Napp's use of the opinions of Max reflected the views in a fair, balanced or accurate way and should not be used in the support of Napp's argument for the relevance of single dose studies in the comparison of analgesics.

Sanofi Winthrop disagreed with the interpretation that Napp made of the Toner clinical summary. Sanofi Winthrop submitted that the relatively small difference between the groups, the wide standard deviations and the p values of between 0.17 and 0.82 did not in any way support Napp's conclusion. A more accurate interpretation of the results, particularly when taken in the overall context of all clinical studies was, as stated in the technical brochure, that:

"No significant differences were seen in VAS [Visual Analogue Scale] and VRS [Verbal Rating Scale] pain scores, patient diary ratings or use of rescue medication".

PANEL RULING

The Panel noted that Morcap SR was licensed for the prolonged relief of chronic, moderate to severe pain. It was not licensed for acute administration. The Panel therefore questioned the clinical relevance of the single dose studies referred to by Napp. The Panel noted from the steady state data provided in the technical brochure that Morcap SR had a pharmacokinetic profile which allowed it to be given once daily whereas modified release morphine tablets did not. Plasma morphine levels with Morcap SR once daily rose relatively slowly but also declined slowly so that reasonably high plasma levels of the medicine were maintained for some hours. By comparison, modified release morphine tablets produced rapid peaks and troughs in plasma morphine and so needed to be given twice daily. The Panel considered it reasonable for Sanofi Winthrop to claim that, in terms of pharmacokinetics, its product was superior compared to modified release tablets. The Panel did not consider, however, that Sanofi Winthrop had implied that its product was clinically superior. The promotional material clearly stated that in terms of efficacy and tolerability the two formulations of morphine were comparable.

The Panel did not consider that the pharmacokinetic data had been presented in an unbalanced or misleading way and ruled no breach of Clause 7.2 of the Code. In addition the claim that Morcap SR had a superior pharmacokinetic profile had not been used in such a way as to imply a clinical advantage and so no breach of Clause 7.3 was ruled.

C Graphical comparison of Cmax

This allegation referred to a graph in the GP mailer headed "Mean plasma morphine concentration against time at a steady state".

COMPLAINT

Napp alleged that the graphical comparison of the 0.75 Cmax for Morcap SR and MST Continus was not clear, fair and balanced. A breach of Clause 7.6 of the Code was alleged.

The basis of Sanofi Winthrop's calculation of the duration of each product above 75% of peak concentration was not clearly stated. However, it appeared from the line on the graph that Sanofi Winthrop had calculated the 0.75 Cmax for 24 hourly Morcap SR and then measured MST Continus tablets 12 hourly against the Cmax for Morcap SR, rather than against the Cmax for MST Continus tablets. The alternative interpretation from the graph was that Sanofi Winthrop had only measured the 0.75 Cmax for MST Continus tablets against its first peak and had not included the second peak in the 24 hour period in the calculation. Either way would not be a fair comparison as it would not reflect the picture over the 24 hour period. The correct measure should be to take the 0.75 Cmax for each of the two peaks for MST Continus tablets added together as a comparison against the 24 hour Morcap SR product.

RESPONSE

Sanofi Winthrop said that the graph was adapted from the study by Gourlay (1995) which reviewed the pharmacokinetic profile of 24 hourly Kapanol [Morcap SR] compared to 12 hourly MST Continus.

In this study the comparison was between 1000mg per 24 hours for Morcap SR and 500mg per 12 hours for MST Continus. The plasma morphine concentration over 24 hours for Morcap SR was represented by a solid blue line. The Cmax occured at between 8 and 10 hours and the 0.75 Cmax for Morcap SR was represented by the dotted blue line.

For the 12 hourly MRMST, the plasma morphine concentration over the 24 hours was represented by the continuous yellow line. The Cmax within the 24 hours occured at approximately 4 hours and the 0.75 Cmax for the MRMST was represented by the dotted yellow line. The legend directly beneath the graph stated what the different lines represented.

The period of observation was 24 hours, a standard time interval. In clinical pharmacology by definition, the Cmax was the maximum concentration reached within the observation period. The graph compared two drugs at a steady state, at dosage intervals which reflected their clinical usage. For clinicians interested in the pharmacokinetics, the important value for Cmax was the highest level reached at steady state during a 24 hour period at a constant dosage reimen. Therefore, the Cmax for MRMST and for Morcap SR was taken as the maximum plasma concentration reached in the 24 hours at a steady state. This most accurately reflected the clinical situation.

The graph accurately reflected the study. It demonstrated the fluctuation of Morcap SR and MST Continus within a 24 hour period in a clear, fair and balanced representation of the pharmacokinetic data.

PANEL RULING

The Panel noted that the author of the study from which the graph in question had been adapted had reported that in a pharmacokinetic comparison of a product equivalent to Morcap SR, given once daily, and modified release morphine tablets, given twice daily, there was no significant difference in the Cmax for the two formulations over a 24 hour dosing period. The Panel considered, therefore, that 0.75 Cmax for both products would also be similar. The graph in question showed a horizontal line at the level of 0.75Cmax for each of the two products. The lines were very close together. From the graph in the GP mailer it could be seen that the length of time plasma morphine levels were equal to or greater than 0.75Cmax was significantly greater for Morcap SR than for the modified release tablets. The Panel considered that the graph had accurately reflected the 24 hour pharmacokinetic profile of both products as reported in the study and ruled no breach of Clause 7.6 of the Code.

D Sustained release profile

This allegation referred to the technical brochure.

COMPLAINT

Napp alleged that Sanofi Winthrop implied that MST Continus was not a true sustained release product. A number of published papers clearly showed the contrary. The claim was unfounded, misleading and disparaging.

Breaches of Clause 7.2 and 8.1 were alleged.

Napp drew attention to the following claims in the technical brochure. "In this key study, Morcap SR exhibited a true sustained-release profile, with small variations between peak and trough levels. This was in contrast to the blood level profiles for both the solution and MRMST" which appeared on page 18 and "The pharmacokinectic studies demonstrate that Morcap SR has a true sustained-release profile" which appeared in the efficacy section on page 20.

Napp also made the following additional comments.

1 Sanofi Winthrop's definition of a "true sustained-release profile", as stated on page 9 of the technical brochure, was "the aim of any sustained-release morphine preparation is to provide even plasma levels for the entire dosing interval". A more appropriate test must surely be whether a product provided effective analgesia throughout the dosing interval as this was the only test which was actually of any consequence to doctor and patient, and accordingly was the only test relevant in a promotional context. However, even if Napp was to adopt Sanofi Winthrop's test and measure its own product against it, Morcap SR 24 hourly fell a long way short of the ideal as it had considerably more fluctuation in plasma levels than when dosed 12 hourly.

2 The study referred to on page 18 of the technical brochure from which Sanofi Winthrop's claim of a "true sustained-release profile" was derived, related only to 12 hourly Morcap SR, the statement on page 20 encompassed both 12 hourly and 24 hourly Morcap SR and so was misleading. It was also notable that this claim of a true sustained release profile was made in a section dealing with clinical effiacy which supported the allegation in point B above that claims of clinical benefit were being implied by the comparison of the sustained release profiles of Morcap SR and MST Continus tablets.

3 The use of the words "in contrast" in the passage quoted from page 18 of the technical brochure clearly implied that MST Continus tablets did not exhibit a true sustained release profile. Since the launch of MST Continus tablets 16 years ago, there had been at least 100 English language publications documenting the efficacy and safety of the preparation. These studies, and in particular ten randomised, double blind, comparative studies in patients with cancer pain, confirmed the efficacy over the full 12 hour dosing interval.

The data provided to Napp by Sanofi Winthrop showed that Morcap SR 12 hourly, in respect of which the claim of a "true sustained-release profile" was made, was less effective than MST Continus tablets mg for mg. A long term safety evaluation study reported that the products were equally effective and yet the mean dosage of Kapanol (equivalent to Morcap SR) 12 hourly used (140mg) was 25% greater than the mean dose of MS Contin (equivalent to MST Continus tablets) used (112.3mg) to achieve the same effect. The suggestion that the Napp product did not have a true sustained release profile therefore ran in the face of the clinical evidence. It was a well established principle that clinical evidence carried more weight than pharmacokinetic evidence when comparisons were being made between different preparations. Even more significant, however, was the clinical evidence that the product with the flatter pharmacokinetic profile was actually less effective.

RESPONSE

Sanofi Winthrop submitted that the fact that Morcap SR was a modified release product was a statement of fact reflected in the SPC. Sanofi Winthrop fully recognised that MST Continus was a modified release product and had no interest nor wish to state the opposite.

The claim that Morcap SR was a true sustained release product appeared twice in the technical brochure. On page 18 a comparison was made with other morphine preparations. This comparison needed to be taken in the context of a 45 page technical brochure under the section of "Pharmacokinetic Studies".

Directly underneath this claim was a graph comparing Morcap SR q12 hrs, MRMST q12h and Morphine solution q4h, where it could be seen that the concentration curve for Morcap SR over 12 hours was considerably flatter than for the comparator modified release morphine product or for the morphine solution.

It was not logical to consider that the "in contrast" referred to the MRMST being a sustained release product and it could only apply to the profiles because the solution cannot be a true sustained release product and therefore the "in contrast" must refer to the variation in the pharmacokinetic profiles represented in the graph under the statement.

Sanofi Winthrop had no intention for the words "in contrast" to imply that the comparator product was not a sustained release preparation. Without prejudice to the consideration of the complaint, and not accepting a breach of the Code, Sanofi Winthrop had recognised that the wording could be misunderstood and therefore in the new version of the techinical brochure the words "in contrast" had been removed to avoid misinterpretation.

Sanofi Winthrop commented as follows on the additional points raised by Napp.

1 The conclusion that Morcap SR was a true sustained release product was based on its pharmacokinetic profile and fulfilled the criteria for sustained release products as detailed by Rang *et al*, Roger *et al* and Squire *et al*. It was reflected in its SPC where it was described as a "modified release capsule".

2 The pharmacokinetic profile of 12 hourly dosing of Morcap SR was different to that of 24 hourly dosing reflecting the different dosing intervals. This was recognised as inevitable by clinical pharmacologists. This did not take away from the fact that Morcap SR was still a "true sustained release" product. If one took Morcap SR 12 hourly or 24 hourly, its release mechanism would not alter. This was reflected in the SPC which stated that Morcap SR could be administered once or twice daily.

3 Napp's interpretation of the clinical data to derive the conclusion that MST Continus was 25% more effective was unbalanced and did not reflect the clinical data or either the one trial quoted or the overall trial evidence.

The figures quoted by Napp were provided by Sanofi Winthrop in response to a request for further details concerning the patient dosages of the six studies quoted in the promotional materials. A summary of the patient dosage details was provided by Sanofi Winthrop and was clearly presented to Napp along with full study details which had been provided in response to previous requests.

Sanofi Winthrop submitted that Napp had extracted part of the total data, taking out of context the Morcap SR q12hr and the MST Continus from the safety evaluation data. Studies by Gourlay, Toner and Kerr had not been taken into account by Napp. The comments from Napp did not represent a balanced, fair and representative selection of the available data as the data Napp referred to included only 26 out of nearly 400 patients for whom a comparison could be made.

The study referred to by Napp had patients on a wide range of morphine doses, a fact reflected by the large standard deviations. It turned out that the patients on MST Continus were taking a lower dose of morphine compared to 12 hourly Morcap SR. It was on this basis that Napp made its point. This ignored the fact that patients on Morcap SR, once daily, were taking a lower dose than either of the two other preparations. Neither of these differences were statistically significant nor in keeping with the overall picture of this study or the other available studies and so Sanofi Winthrop made no claims about the relative effectiveness of 24 hourly Morcap SR.

Taking all the studies where MST Continus and Morcap SR had been compared gave the following dosage for the two products: Morcap SR 148mg (222 patients) MST Continus 154.5mg (161 patients).

Sanofi Winthrop submitted that the data showed that over all the studies the dosages of the two products were very similar with, if anything slightly lower rather than higher dose required for Morcap SR. Given that the values were so similar, Sanofi Winthrop made no claim concerning Morcap SR being more efficacious.

A balanced and representative interpretation of the available information drew the conclusion that was consistently made in Morcap SR materials by use of phrases that Morcap SR "controls pain as effectively as a MRMST" and has "comparable efficacy and tolerability".

PANEL RULING

The Panel considered that the claim "... Morcap SR exhibited a true sustained-release profile, with small variations between peak and trough levels. This was in contrast to the blood level profiles for both the solution and MRMST" was ambiguous and could be taken to mean that Morcap SR was truly a sustained release preparation whilst the other two products were not. The use of the phrase "This was in contrast to ..." threw doubts as to the sustained release profile of modified release morphine sulphate tablets which was misleading. The Panel noted that Sanofi Winthrop had already recognised that the wording could be misunderstood and in a new version of the brochure the words "in contrast" had been taken out. A breach of Clause 7.2 was ruled. The Panel did not believe that the claim was disparaging of MST Continus tablets per se and so ruled no breach of Clause 8.1.

The Panel considered that the claim "The pharmacokinetic studies demonstrate that Morcap has a true sustained-release profile" was one of fact. Although this statement appeared under an "efficacy" heading in the brochure, the Panel noted that no comparison to any other product was being made and nor was any implied. The Panel noted that no clinical benefit was attributed as a result of the pharmacokinetics of Morcap SR. Immediately above the statement was a highlighted box which contained a claim that Morcap SR, once or twice daily, was as effective in pain control as modified release tablets. No breach of Clause 7.2 was ruled.

E Use of patient global assessment

This allegation referred to the technical brochure, the "Dear Doctor" and "Dear Nurse" letters and the GP mailer. The claims were referenced to a study by Kerr.

COMPLAINT

Napp alleged that the use of a patient global assessment in one of Sanofi Winthrop's trials was unbalanced and misleading as it gave it undue prominence and significance bearing in mind the evidence from other studies. A breach of Clause 7.2 of the Code was alleged.

Napp said that the claim on page 21 of the technical brochure "Significantly more patients rated pain control as 'good' or 'very good' with Morcap SR" was also made

in the "Dear Doctor" and "Dear Nurse" letters and the GP mailer.

Napp made the following points:

1 This claim was based upon a study conducted by Kerr R O *et al*, 1995. Significantly in this parallel group study, patients received only Morcap SR 12 hourly or Morcap SR 24 hourly or MST Continus tablets 12 hourly. There was no crossover of treatment. Accordingly, none of the patients in the study were in a position to compare the preparation which they were receiving with the other two. It was notable that the investigators, who were in the most qualified position to make a comparative judgement of the three treatments, did not record any significant difference between the treatments in their own global assessment.

2 The patients receiving the respective treatments would have included individuals with varying degrees of pain. There was no evidence in the Kerr study that patients were titrated to the same degree of baseline pain. Without this, the patient global assessment was of no value whatsoever as the patient ratings could have been more a reflection of their different levels of pain prior to treatment, rather than any reflection of different efficacy of treatment.

3 It was notable that in the crossover rather than parallel group studies conducted by Sanofi Winthrop where patients were able to compare the respective treatments, no statistical differences were found. The Gourlay study comparing 24 hourly Morcap SR and MST Continus tablets reported no difference between the preparations on patient global assessment. In addition, the Toner study, which was also a crossover study, did not report whether a global assessment was conducted, but, as mentioned above, it was noticeable that the trend of the results was towards better analgesia with the instant release morphine.

4 It was odd that there was no significant difference in patient global assessment between MST Continus tablets and Morcap SR 12 hourly, which had a flatter, and by Sanofi Winthrop's standards a "superior", pharmacokinetic profile than Morcap SR 24 hourly. This contradicted the statement in the "Dear Doctor" and "Dear Nurse" letters that the pharmacokinetic profile of the 24 hourly product was the cause of more patients rating that preparation "good" or "very good". If this were the case then the patient global assessment should have shown a significantly higher rating for Morcap SR 12 hourly over both Morcap SR 24 hourly and MST Continus tablets.

RESPONSE

Sanofi Winthrop gave details of the promotional material in question as follows:

The technical brochure stated on page 21 that "There was no significant difference between the groups with regard to VAS [visual analogue scale] for pain intensity and VRS [verbal rating scale] data for both pain intensity and pain control. In addition, there was no differences between groups with regard to quality of sleep. Patient global assessment of pain control scores significantly favoured the Morcap SR 24 hourly group as opposed to the MRMST group. While the investigator global assessment scores were also higher for 24 hourly Morcap SR, the between group was not statistically significant".

The "Dear Doctor" and "Dear Nurse" letters stated that Morcap SR's novel sustained-release mechanism ensured a superior pharmacokinetic profile in comparison to a currently available 12 hourly modified-release product. This in turn allowed once-daily dosing with comparable efficacy and tolerability which more patients rated "good" or "very good".

The GP mailer stated that Morcap SR "Controls pain as effectively as a MRMST", "Similar incidence of breakthrough pain or need for rescue medication", and significantly more patients rated pain control as "good" or "very good" with Morcap SR".

Kerr *et al* performed a double-blind, randomised, double-dummy parallel group study in 172 patients with moderate to severe cancer pain. He randomised patients to Morcap SR, given every 12 to 24 hours, or MST Continus, given every 12 hours for seven days (plus or minus one day). 152 patients completed the study. Primary efficacy assessments on the final day were: time to rescue medication and total amount of rescue medication taken over the final 24 hours of the study period.

The patient's global assessment of pain control and the investigator's global assessment of efficacy were evaluated on the final day of treatment. There were also the daily efficacy assessments during the study time, where pain intensity was evaluated using a visual analogue scale and verbal rating scale and pain control was evaluated using a verbal rating scale. Information on quality of sleep was also collected during this period.

The results from the time to rescue medication, total amount of rescue medication, the VAS for daily pain intensity and VRS data for both daily pain intensity and daily pain control revealed no statistically significant difference between the groups and therefore no claims for the effectiveness of the analgesia were made other than Morcap SR "controls pain as effectively as a MRMST".

Patient global assessment of pain control was assessed on the final day of treatment. It was a well accepted measure of patient assessment and was frequently used as it was recognised that, particularly in cancer pain, there were a multitude of factors affecting pain control. In the study by Kerr there was a significant difference in favour of 24 hourly Kapanol in the patient global assessment. Being a large, well designed clinical trial, it was reasonable for Sanofi Winthrop to use the data in a balanced way which truly reflected the study.

Pages 21-22 of the technical brochure clearly stated that objective pain assessments were the primary efficacy parameters. Consequently these were the results which were presented first by means of inclusion in separate tables from secondary efficacy data such as patient global assessment. This reflected the balanced approach to the presentation of the data of this important study.

The same principle was applied in the "Dear Doctor", and "Dear Nurse" letter and the GP mailer. The primary efficacy points were presented first, with the patients' global assessment results presented in the context of the study. In each of the above, the expressions "comparable

efficacy and tolerability", "similar incidence of breakthrough pain or need for rescue medication" and "controls pain as effectively as a MRMST" were always stated first, as in the study protocol.

Sanofi Winthrop commented as follows on the additional points raised by Napp.

1 Sanofi Winthrop argued that the most qualified person to assess a global assessment of pain control was the person who was actually experiencing the symptoms. The objective measurements of time to rescue medication and amount of rescue medication were acceptable primary end points. However, in line with common practice, the overall "global assessment of pain control" was an important adjuvant to these primary end-points and as such could therefore be reported provided it was in the context of the primary analgesic data.

In a parallel study design, comparisons were, by definition made between groups. When randomised and double-blinded this design had some significant advantages over crossover studies particularly under circumstances, such as with cancer patients, where there may be significant temporal changes.

2 With opiate administration for the relief of cancer pain, the range of dosage required would inevitably be great depending on the extent and spread of disease. This was reflected in the Kerr study where the standard deviation over 152 patients was well over 100mg. Sanofi Winthrop disagreed with the suggestion by Napp that: "Without titration to the same degree of baseline pain the patient global assessment is of no value whatsoever as the patient ratings could have been more a reflection of the different levels of pain prior to treatment, rather than any reflection of different efficacy of treatment". This might be true for a open non-randomised study, but the study design used by Kerr, by means of randomisation, addressed this problem. It was a double-blind, randomised, double-dummy design which allowed an even distribution of patients with varying pain levels in each group. That randomisation allowed for a balanced distribution, was reflected in the mean dosage in the three groups over 24 hours which was 134.8mg for Morcap SR q24 hours, 141.2mg/24 hours of Morcap SR q12h and 138.5mg for MST Continus. Furthermore, "all eligible patients were titrated to adequate analgesia... during a 3-14 day lead in period". Patients were titrated to adequate analgesia, and the dosages required were similar in the two groups strengthening the legitimacy of comparison.

The results quoted in the promotional material had statistical significance, $p<0.05$.

3 The study by Kerr was one of the largest and best designed of its type. Its results were in keeping with other studies, but owing to its size, was able to reach statistical significance (n=152 in the study by Kerr, n=24 in the study by Gourlay).

PANEL RULING

The Panel noted that the study from which the patient assessments had been taken was a double-blind study in 172 patients (152 patients completed the study). The Gourlay study which showed no difference between Morcap SR and modified release morphine sulphate tablets in terms of patient assessment involved only 24 patients. In the Panel's view the study which had been used was large enough for the results to be meaningful. The Panel considered that readers would understand the limitations of such data but nonetheless thought it was not unreasonable for it to be used in promotional material. The Panel did not consider that the use of the patient global assessments was either unbalanced or misleading and so ruled no breach of Clause 7.2.

F Dosage

This allegation referred to the technical brochure and to the conversion leavepiece.

COMPLAINT

Napp drew attention to a claim on page 22 of the technical brochure "Morcap SR given every 12 hours or every 24 hours was as effective as MRMST given every 12 hours in maintaining pain control...". The conversion leavepiece claimed that Morcap SR was "straightforward to use". Napp alleged that the claim in the detail aid did not accurately reflect the data and the claim in the conversion leavepiece failed to address the lack of equivalent strengths. Both claims were misleading in breach of Clause 7.2.

Napp made the following additional points:

1 Point D above provided details of the respective doses of the equivalent products to Morcap SR and MST Continus tablets which were used in the long-term safety evaluation study data on file cited as a reference in the technical brochure. The mean dosing data showed that 25% more Morcap SR was required to produce the same effect as MST Continus tablets. The claim at issue in this allegation from the technical brochure was based upon the same trial. In not pointing out the need for higher dosing of Morcap SR 12 hourly, Sanofi Winthrop's claim was misleading.

2 The strengths of Morcap SR and MST Continus tablets avaiable were very different. MST Continus tablets were available as 10mg, 15mg, 30mg, 60mg, 100mg and 200mg tablets, whilst Morcap SR capsules were available only as 20mg, 50mg and 100mg capsules. The only equivalent strength, therefore, was 100mg.

The conversion leavepiece contained a recommendation to doctors to convert patients from existing morphine preparations to Morcap SR, but failed to address the non-availability of equivalent strengths. This meant that Sanofi Winthrop's claim that its product was "straightforward to use" was misleading when applied to the conversion of patients already receiving controlled release morphine. This was not helpful to doctors.

RESPONSE

Sanofi Winthrop submitted that there were two distinct complaints which it would respond to in turn. Dealing first with the technical brochure which included the following claims.

"This study confirmed that sustained-release Morcap SR ... is as effective for controlling cancer pain as immediate-release morphine sulphate solution ..." (page 20)

"There was no statistical difference in the incidence of breakthrough pain and hence use of rescue medication between Morcap SR ... and MRMST." (page 21)

"In a multicentre bioavailability study comparing Morcap SR, given every 24 hours, with MRMST given every 12 hours in patients with moderate to severe chronic cancer pain both compounds provided an equivalent degree of pain relief with the same profile of morphine-related side effects." (page 22)

Sanofi Winthrop pointed out that Morcap SR was as effective as MST Continus and this was borne out by clinical trials and was reflected in the SPC.

As discussed under point D above, Napp had presented the trial data in an unbalanced manner despite being provided with the full information concerning the comparative studies between Morcap SR and MST Continus.

A balanced and representative interpretation of the available information drew the conclusion which was consistently made in the Morcap SR materials by use of phrases that Morcap SR "controls pains as effectively as a MRMST" and has "comparable efficacy and tolerability". This was reflected in the SPC for Morcap SR where it described the conversion from other oral morphine formulations to Morcap SR.

> "Patients on other oral morphine formulations may be converted to Morcap SR by administering one half of the patient's total daily morphine dose as Morcap SR capsules on an every 12 hours dosing regimen, or by administering the total daily morphine dose as Morcap SR capsules on an every 24 hours dosing regimen. Dose is then adjusted as needed."

With regard to the claim that Morcap SR was "Straightforward to use", Sanofi Winthrop referred to the following promotional items:

"Dear Doctor" and "Dear Nurse" letters with the claim "... its use is straightforward, with three clearly identifiable strengths (20, 50 and 100mg) allowing precise titration."

Conversion leavepiece where the words "straightforward to use" appeared above a table describing the conversion from 4 hourly and 12 hourly preparations to once daily Morcap SR.

All claims relating to the "straightforward" nature of conversion referred to the conversion to once daily Morcap SR and it was this conversion which was therefore discussed. All permutations of dosage regimens were catered for and there was no situation where there was a lack of equivalent strength for this conversion.

Immediate release morphine (given 4 hourly) was available in strengths of 10, 20 and 50mg; MST Continus (given 12 hourly) was available in strengths of 10, 15, 25 and 50mg; Morcap SR (given 24 hourly and also licensed for 12 hourly prescription) was available in strengths of 20, 50 and 100mg.

The conversion leavepiece included a chart to aid healthcare professionals in conversion of patients from immediate release morphine to once daily Morcap SR. Sanofi Winthrop provided two dosage conversion tables to support its submission.

The tables showed that conversion from any dose of immediate release morphine solution or modified release morphine preparation lent itself to a combination of capsule strengths catered for by once daily Morcap SR. It was the once daily dosage frequency which was referred to in the promotional material. There was also the immense added ease of use by the reduction from taking a medicine twice a day or six times a day, to taking it only once-daily. Additionally, for each Morcap SR once daily regimen, at no dosage was the patient required to take a greater number of tablets in the day, compared with the 4 hourly or 12 hourly regimens, thereby making the switch straightforward for the patient as well.

In conclusion, the process of converting from 4 hourly or 12 hourly morphine to 24 hourly Morcap SR was a simple conversion. It was fair to state that clinicians would find it "straightforward" and there were equivalent doses available for all the possible combinations of IRM and MST Continus.

PANEL RULING

The Panel noted that Sanofi Winthrop had provided data, which had previously been supplied to Napp, to the effect that Morcap every 12 or 24 hours and modified release morphine sulphate tablets every 12 hours were clinically equivalent on a mg for mg basis. A metaanalysis of almost 400 patients showed that the average dose of Morcap SR required was 148mg while that for MST Continus was 154.5mg. The data referred to by Napp was a sub-set of all the available data and represented the clinical results from only 26 patients. In the Panel's view the claim that Morcap SR was as effective as modified release morphine sulphate tablets was not inaccurate and no breach of Clause 7.2 was ruled.

The Panel noted that Sanofi Winthrop in its response referred to MST Continus tablets as being available in strengths of 10, 15, 25 and 50mg. The tablets were in fact available in strengths of 10, 15, 30, 60, 100 and 200mg (ref MST Continus data sheet, ABPI 1996-97 Compendium). In addition Sanofi Winthrop, in one of the tables elaborating dosage conversion supplied in its response to the Authority, referred to a 10mg dose of Morcap SR whereas the capsules were only available in strengths of 20, 50 and 100mg (ref Morcap SR SPC). The Panel noted that Sanofi Winthrop had submitted that conversion from any other form of oral morphine was straightforward as there was no situation where there was a lack of equivalent strength for this conversion. The Panel noted that although MST Continus tablets were available in a number of strengths, and could be given in various combinations, very few situations would arise when there would be no direct equivalent strength of Morcap SR either given as a single capsule or as a combination of the 20, 50 and 100mg capsules.

The Panel noted that the conversion leavepiece promoted Morcap SR once daily. The claim "Straightforward to use" appeared above a table which laid out how to start patients on Morcap SR from a base of no opioids, immediate release morphine or modified release morphine tablets. For patients taking oral morphine, their

total daily dose could be administered as Morcap SR once daily. The Panel noted that there were only very few doses of modified release morphine sulphate tablets which could not be directly converted to the equivalent dose of morphine as Morcap SR, ie 15mg twice daily, but did not consider that the heading "Straightforward to use" implied an exact equivalent of Morcap for every dose of oral morphine a patient could be taking. The Panel had some concerns about the claim "Straightforward to use" as it was not clear whether it was intended to mean that Morcap SR was straightforward for the patient or for the prescriber. There would be advantages for the patient and the doctor in using a once daily preparation. On balance, the Panel considered that the claim was not misleading and no breach of Clause 7.2 of the Code was ruled.

G References to side effects

This allegation referred to the technical brochure.

COMPLAINT

Napp drew attention to page 10 of the technical brochure which stated that the absorption profile of Morcap SR differed markedly from MST Continus tablets. "As a result, the concentration-time curve is flatter and peak serum concentrations not achieved until 7-9 hours after dosing .... potentially reducing side effects related to plasma morphine levels".

There was no evidence to support the claim that there were potentially less side effects with Morcap SR than with MST Continus tablets. All of the evidence from clinical trials which Sanofi Winthrop had conducted contradicted this claim as they showed no difference in the side effect profile of the two preparations. As Sanofi Winthrop was unable to substantiate this claim, it was misleading. Breaches of Clause 7.2 and 7.3 of the Code were alleged.

RESPONSE

Sanofi Winthrop submitted that when taken in context, the claim of potentially reducing side effects relating to plasma morphine levels was made appropriately and supported by its current understanding of clinical pharmacology.

The statement that the absorption profile of Morcap SR differed markedly from that of both oral morphine solution and modified release morphine sulphate tablet (page 10) was only located in a section discussing the clinical pharmacology of morphine, specifically absorption and bioavailability. It was appropriate to discuss pharmacology and widely supported pharmacokinetic theory in this context, ie a 45 page document providing extensive background and product related information for health care professionals.

It was generally accepted that the flatter concentration-time curves produced by a sustained release formulation might potentially be associated with fewer of the adverse effects caused by high peak drug plasma concentrations and with reduced symptom breakthrough caused by trough drug plasma concentrations.

This was confirmed by a number of publications.

> "(Sustained release) preparations can ... reduce adverse effects related to high peak plasma concentrations following administration of a conventional formulation" (Rang HP, Dale MM, Ritter JM (Eds). Pharmacology (3rd Edition).
>
> "A slow release formulation may improve patient compliance and theoretically, by maintaining a continuous blood level, should prevent symptom breakthrough. In the case of some drugs ... effects due to high peak plasma concentrations may be avoided" (A Textbook of Clinical Pharmacology, Ed Gillies HC *et al*).
>
> "Advantages of controlled release preparations:
>
> Reduction of fluctuation in plasma concentration:
>
> → prolonged maintenance of therapeutic drug levels
>
> → reduced side effects from toxic drug levels
>
> → reduce symptom breakthrough"
>
> (Taken from Squire I, Lees K: Slow release delivery systems, The Practitioner, November).

Sanofi Winthrop submitted that the Morcap SR technical brochure reflected the above statements when it stated:

> "Absorption of Morcap SR is controlled by the polymer coating of each morphine sulphate pellet, leading to an extended absorption phase. As a result, the concentration - time curve is flatter and peak serum concentrations are not achieved until 7-9 hours after dosing potentially reducing the side effects related to plasma morphine levels".

The shorter Oxford English Dictionary defined "potential" as meaning "possible, as opposed to actual", further supporting the statement in the Morcap SR technical brochure.

PANEL RULING

The Panel accepted that, as a pharmacological principle, controlled release preparations, by avoiding the extreme peaks and troughs seen with immediate release products, might be associated with a reduced incidence of side effects. The Panel considered, however, that explaining such a principle in relation to Morcap SR amounted to a positive claim for the product. The claim had appeared at the end of a paragraph comparing Morcap SR with immediate release morphine and modified release tablets and so would be taken to mean that Morcap SR had a reduced incidence of side effects in comparison to both of these products. In comparison, the Panel noted that on page 22 of the technical brochure was the statement "Morcap SR ... every 24 hours was as effective as MRMST given every 12 hours ... with no difference in the incidence or severity of morphine-related side effects". In addition the "Dear Doctor" and the "Dear Nurse" letters also referred to the "comparable ... tolerability" of the two products.

The Panel noted that the Morcap SR SPC contained the statement that the peak morphine plasma levels following administration of Morcap SR once daily were significantly higher than if the product were administered twice daily. While clinical studies had shown no difference in morphine related side effects between the two dosage

regimens, the possibility of increased side effects with the 24 hourly regimen could not be discounted. In the Panel's view the claim in the technical brochure did not fully reflect the information given in the SPC.

The Panel considered that the statement as written was ambiguous and misleading with respect to the comparison of Morcap SR and modified release morphine sulphate tablets. The statement was based on pharmacological principles and failed to reflect clinical experience. The Panel ruled a breach of Clause 7.2.

Complaint received 19 December 1996

Case completed 11 March 1997

CASE AUTH/487/1/97 *NO BREACH OF THE CODE*

DIRECTOR OF PRIMARY CARE MEDICINE v GEIGY

Voltarol advertisement

A health authority director of primary care medicine alleged that a festive journal advertisement listing items provided to practices, such as meetings, pens, model joints and useful books, issued by Geigy could be seen as a bribe to use Voltarol.

The Panel ruled no breach of the Code. The Panel had some sympathy with the complainant's concerns but did not consider that the advertisement amounted to an inducement to use the product.

A health authority director of primary care medicine, complained about an advertisement for Voltarol issued by Geigy Pharmaceuticals which appeared in Pulse, 14 December, 1996. The advertisement took a festive theme. It began with the phrase "On the 12th day of Christmas Volt-a-rol gave to me" and went on in a similar vein to the Christmas song to list various benefits of Voltarol and the support services provided by Geigy.

COMPLAINT

Although recognising that this was intended as a light-hearted festive advertisement, the complainant considered that it was inappropriate. It appeared to suggest that Geigy provided free, to practices, meetings, pens, model joints and useful books. This could be seen as an overt bribe to use the product.

Referring to the last line "and a simple prescription for me," the complainant was not quite certain who the "me" was in this regard. Was the prescription simple for the patient or merely simple for the prescriber?

The complainant had grave reservations about the appropriateness of the advertisement.

RESPONSE

Ciba Pharmaceuticals, responding on behalf of Geigy, submitted that the Voltarol advertisement was intended to be a light hearted festive piece to remind the reader of the benefits of Voltarol and of the support services provided by the company for the medical profession. Similar to many other pharmaceutical companies, Ciba provided these support items in accordance with the Code as aids to the practice of medicine. As a result, Ciba believed these items could not be considered a bribe to use the product or to generate a request for an interview.

The details of the advertisement were factual, referring to the licensed indication and the breadth of dosage strengths, formulations and pack sizes available. This diversity could assist the physician in his choice of treatment for a particular individual and could offer enhanced patient compliance.

Ciba submitted that the advertisement was in good taste and appropriate to the intended audience. Ciba said that this view was supported by the fact that only a single complaint had been brought to its notice despite the advertisement appearing for two consecutive years in Pulse.

With regard to the "and a simple prescription for me" Ciba referred to the fact that Voltarol 75mg SR could be given as a simple once or twice daily dose which could allow the physician to make an appropriate prescribing choice. The intention was therefore that "me" referred to the physician to whom journals such as Pulse were targeted.

PANEL RULING

The Panel noted that gifts of pens, model joints and books etc were permitted by the Code provided that the requirements of Clause 18 were met. Similarly, meetings could be sponsored provided that the requirements of Clause 19 were met. There was no reason to deduce from the advertisement that the Code would not be complied with in these respects.

The Panel had some sympathy with the complainant's concerns but did not consider that the advertisement in any way amounted to an inducement to use the product. It was a seasonal item and the Panel considered that its use was acceptable and ruled that there was no breach of the Code.

It was, however, agreed that it should be pointed out to Ciba that, in the Panel's view, having referred to the proposed gifts in a promotional item, they could not come within the supplementary information to Clause 18.1 which related to the provision of non-promotional medical and educational goods and services.

Complaint recevied 6 January 1997

Case completed 12 February 1997

CASE AUTH/489/1/97

NO BREACH OF THE CODE

ANON v BAYER

Ciproxin advertisement

An anonymous complainant alleged that a journal advertisement issued by Bayer constituted disguised promotion. The advertisement was headed "Advertorial feature".

The Panel ruled no breach of the Code. The layout and design of the page was different to that used in editorial material.

COMPLAINT

An anonymous complaint was received regarding an advertisement in Hospital Doctor, 9 January 1997. The complainant alleged that the advertisement was in breach of Clause 10.1 of the Code.

The advertisement itself was on two pages. The right hand page was headed "Advertorial feature" and discussed hospital acquired pneumonia. It referred to ciprofloxacin (contained in Bayer's product Ciproxin) and also to other antibiotics. The prescribing information appeared in the far right hand column of the left hand page.

RESPONSE

Bayer did not accept that the advertisement was disguised promotion. The article was clearly headed "Advertorial feature" and full prescribing information was included. In addition, the advertisement did not copy the usual text format in terms of type size, type face, column layout and colour of headers usually reserved for editorial pieces in the journal.

PANEL RULING

The Panel noted that the use of advertisements like the one at issue in this case was becoming more common.

The supplementary information to Clause 10.1 required that advertisements should not resemble editorial matter.

In this particular case, the Panel noted that although the page was headed "Advertorial feature" this heading appeared in a very small type size. The layout and design of the page were, however, quite different to that used for the editorial material in that wider columns had been used and the illustrations had been placed at an angle. The Panel considered that this advertisement was at the limits of acceptability in relation to Clause 10.1 but decided that in this particular instance there was no breach of the Code.

Complaint received **22 January 1997**

Case completed **30 January 1997**

CASE AUTH/490/1/97

NO BREACH OF THE CODE

HOSPITAL INFORMATION PHARMACIST v PARKE DAVIS

Letter offering samples

An information pharmacist at a trust hospital complained about a letter sent by Parke Davis to a doctor at the hospital offering samples of Lipitor (atorvastatin). This conflicted with trust policy which required all supplies of medicines to be initiated and received by the pharmacy department following approval by the drug and therapeutics committee.

The Panel noted that Parke Davis had not in fact supplied any samples to the hospital as it had become aware of the trust's policy following an enquiry. As no samples had been supplied, the Panel ruled that the Code had not been breached. The Panel considered that criticism might have been avoided if the letter to doctors had been more explicit as to the way in which requests would be handled.

This case concerned a letter sent by Parke Davis to certain doctors offering samples of Lipitor (atorvastatin). The letter offered up to ten sample packs and said that they would be delivered to the pharmacy in accordance with usual practice. A form was provided for completion and return.

COMPLAINT

An information pharmacist at a trust hospital complained by way of a copy of a letter which he had sent to Parke Davis complaining about a letter sent by the medical director of Parke Davis to a doctor at the hospital.

The complainant said that the contents of the letter gave him some concern as it seemed to be soliciting prescribing which did not conform to the agreed procedures in place in the trust, contravening Clause 17.8 of the Code.

The trust had an active procedure for the introduction and use of new medicines. This was coordinated by its drug and therapeutics committee and part of this procedure was for all medicine supplies to be initiated and received by the pharmacy department following approval by the drug and therapeutics committee.

Medicine samples or medicines were not accepted as part of a thinly disguised marketing exercise as this might lead, among other undesirable outcomes, to inappropriate use of resources and problems in continuity of patient treatment.

The complainant said that he would be most grateful if Parke Davis immediately withdrew this marketing scheme and also informed any other clinicians that Parke Davis had contacted in the trust that it was not acceptable and that normal procedures should be used.

RESPONSE

Parke Davis said that in preparing this letter to selected specialists, it recognised that despite it being a personal communication, it should be considered promotional in nature and therefore within the scope of the Code of Practice. Parke Davis also went to considerable lengths to be sensitive to local procedures and thus avoid any possible breach of Clause 17.8.

The letter itself informed the doctor that Parke Davis would be involving the hospital pharmacy and the sample request form asked specifically for the pharmacy address and contact name. Following receipt of this completed form, Parke Davis' local hospital representatives were to speak personally to or visit the named hospital contact. This was to confirm that the actual procedure that had to be followed in each hospital to supply the requested samples would be complied with. No samples were to be released unless the requested procedure was compliant with hospital policy.

In the case of the complainant's hospital, four physicians had expressed some interest in using Lipitor at the earliest opportunity. Following the procedure described above, Parke Davis' local representative reviewed this interest with the hospital's cardiopharmacist who explained the trust's local policy and as a result no samples were supplied or placed in the hospital. This had also occurred on a few occasions following pharmacy review at other locations around the country and in every case local policy and procedure had been respected and followed. The mechanisms put in place had worked effectively to ensure that local policies had been followed. Therefore no breach of Clause 17.8 had occurred.

With regard to the distribution of this letter, it was not as the complainant suggested "a thinly disguised marketing exercise". The letter in question was a personal mailing to specific doctors who had previously expressed some interest in working with Lipitor in a clinical trial setting.

To date, the complainant's letter was the only concern that had been expressed. Most doctors were grateful for the information whether or not samples were requested. Parke Davis additionally pointed out that care was taken to ensure that the sample packs provided met all of the "physical requirements" of Clause 17 of the Code, for example, amount, pack size and pack labelling.

PANEL RULING

The Panel noted that Clause 17.8 of the Code stated that "The distribution of samples in hospitals must comply with individual hospital requirements". As no samples had in the event been supplied to the hospital in question, the Panel did not consider that Clause 17.8 of the Code had been breached and so ruled. Parke Davis seemed to have been fully aware of the need to ascertain local requirements and to act accordingly. It might have avoided criticism if the letter to doctors had been more explicit in this respect.

Complaint received **23 January 1997**

Case completed **27 February 1997**

CASE AUTH/491/1/97

GP v ASTRA

Use of gift to gain an interview

A general practitioner complained that an Astra representative had failed to leave an otoscope at his surgery having brought with her the reply paid request card which he had completed. He alleged that the item was not "complimentary" but was made available only to gain access to his time.

The Panel observed that the representative had attended with otoscopes requested by certain of the doctors at the surgery but had not left them, some direct or indirect contact with the recipients having apparently been regarded as a prerequisite. The Panel considered that they were being used as inducements to gain interviews and a breach of the Code was ruled. The cost of the otoscopes was acceptable and no breach was ruled in that regard.

COMPLAINT

A general practitioner said that he was increasingly concerned about a particular marketing method used by a number of companies. The current example concerned Astra Pharmaceuticals Ltd but it was by no means the only one. Astra had sent in a reply paid card offering a "complimentary" otoscope. His understanding of that word was that complimentary meant free, with no strings attached. Astra's representative had visited the surgery and was unwilling to relinquish the otoscope because "it is too expensive". The otoscope was clearly, in this situation, not complimentary. There was a price to be paid for it, namely clinical time, and the loss of an appointment which could have been used by a patient.

There were two aspects to this as the complainant saw it. Gifts were supposed to be inexpensive. He did not know the value of one of the otoscopes, but it was clearly considered to be expensive enough to purchase general practitioner time. There was also an aspect of deceit and this was now being seen increasingly with a number of companies which gave the impression of providing something free, yet this free item was only available on payment of a consultation. The words "free" and "complimentary" as used by pharmaceutical companies

were becoming rather a joke.

The complainant resented the use of manipulative guilt as a dysfunctional mechanism for gaining access to his time. He tended not to see representatives. He would ask for them when he wanted to do so or would ask for information when he needed it or he would talk to them at meetings. Promising free things, particularly not free, was increasingly pervasive.

RESPONSE

Astra investigated the circumstances thoroughly and did not believe that a breach of the Code of Practice had occurred for the following reasons:

i) All Astra representatives were trained in the Code of Practice and it was made clear that if a doctor was unable to personally receive a gift, then it should be left with the receptionist or other appropriate person;

ii) According to the representative concerned, she did not speak to the complainant. She did, however, have reply paid cards from a number of doctors in the practice requesting the otoscope. She asked the receptionist whether it would be convenient to see the doctors with the otoscope. The receptionist advised that she would put the relevant reply paid cards in the respective doctors' trays for them to mark whether or not they wished to see her.

The representative stated that the receptionist did not ask her to leave the otoscope for any of the doctors. Also, the receptionist was not the usual lady who dealt with representatives. The receptionist stated that appointments or otherwise would be made when the "usual" lady returned to work.

The representative stated that she knew she must leave the otoscope with the receptionist if the doctor(s) requested her to do so. She cited examples of situations where she had done this during the previous two weeks.

iii) However, given the complainant's letter, the impression that the representative left was clearly not the desired one. Astra had, therefore, firmly reminded her of its commitment to conform to the Code of Practice. Also, that there needed to be clear communication concerning reception staff whether known to them or not. Astra expected its representatives to conform to the Code of Practice. It was a contractual obligation for them and one which Astra took very seriously.

In response to the Authority's specific questions:

1 The offer was made by a reply paid card attached to a mailing;

2 the cost of the otoscope was £4.78;

3 the representative had passed her ABPI Medical Representatives Examination in 1992;

4 copies of the relevant briefing material sections referring to the delivery of gifts were supplied.

PANEL RULING

The Panel noted that the representative had taken with her to the surgery the reply paid cards completed by certain of the doctors there and had drawn these to the attention of the receptionist.

It was not entirely clear what had transpired thereafter as the accounts given by the complainant and Astra were not at one. What was clear, however, was that the representative had left without leaving any of the requested otoscopes. The Panel did not consider it relevant that she had not been asked by the doctors to leave them. She had attended with the otoscopes and had not left them, some direct or indirect contact with the intended recipients having apparently been regarded as a prerequisite.

The Panel ruled that there had been a breach of Clause 15.3 of the Code as it considered that the otoscopes were being used as inducements for interviews. The otoscope was acceptable as a promotional aid as it cost less than £5 and was relevant to the practice of medicine and there had thus been no breach of Clause 18 of the Code.

Complaint received **24 January 1997**

Case completed **10 March 1997**

CASES AUTH/494/2/97 & AUTH/495/2/97

PHARMACEUTICAL ADVISER v ASTRA

Letters announcing Entocort Enema and Naropin

A pharmaceutical adviser to a health authority complained about two letters sent by Astra Pharmaceuticals announcing the introduction of new products.

The Panel ruled a breach of the Code as one letter gave the product name, Entocort Enema, and a product claim and had not included the prescribing information. The Panel ruled that the second letter, about Naropin, was a trade advertisement as no product claims were made. It was exempt from the Code and no breach was ruled.

COMPLAINT

A pharmaceutical adviser to health authority, complained about material sent by Astra Pharmaceuticals Ltd. The complainant alleged that two letters sent by Astra should have included prescribing information.

Consideration was as follows:

Case AUTH/494/2/97 - Entocort Enema letter

The letter announced the launch of the product including the indication "... for the treatment of ulcerative colitis involving rectal and recto-sigmoid disease".

RESPONSE

Astra submitted that the letter had been intended to be a trade announcement. The company accepted, however, that the letter was in breach of Clause 4.1 of the Code as an indication had been given but prescribing information had not been included. Astra had reviewed its procedures in this regard.

PANEL RULING

The Panel noted that the definition of promotion excluded factual, accurate, informative annoucements provided that they included no product claims (Clause 1.2). The Entocort Enema letter included the product claim, " ... for the treatment of ulcerative colitis involving rectal and recto-sigmoid disease". The letter was therefore not a trade announcement exempt from the requirements of the Code. It was promotional material and prescribing information was required. The Panel ruled a breach of Clause 4.1 of the Code as no prescribing information had been given.

Case AUTH/495/2/97 - Naropin letter

The letter and its attachment announced the launch of Naropin Polyamp and Naropin Infusion. Details of pack sizes and strengths, product codes and prices were provided but no claims were made.

RESPONSE

Astra submitted that the letter was a trade announcement which made no product claims and therefore did not require prescribing information.

PANEL RULING

The Panel noted that the letter itself only gave the product name and launch dates. The letter was accompanied by details of pack sizes and order codes of the particular products. No product claims were made. The Panel accepted the submission from Astra that the letter was a trade announcement exempt from the requirements of the Code. No breach of the Code was ruled.

Complaint received	**5 February 1997**
Case AUTH/494/2/97 completed	**14 March 1997**
Case AUTH/495/2/97 completed	**12 March 1997**

CASE AUTH/496/2/97

NO BREACH OF THE CODE

GP v ZENECA

Prize draw offer as an inducement to purchase

A general practitioner alleged that a competition arranged by Farillon, a wholesaler, to encourage practices to convert suitable patients from Zoladex to Zoladex LA, both Zeneca products, was offensive. The prizes in a quarterly draw would be a first prize of £1,000, a second prize of £100 Marks & Spencer gift vouchers and a third prize of £50 Marks & Spencer gift vouchers. In addition, practices initiating a standing order for Zoladex LA would receive a free bottle of wine.

The Panel noted that Zeneca had considered that such a method of promotion was inappropriate and had tried to bring it to an end. The Panel considered that the prize draw did not come within the scope of the Code as it was not an activity undertaken by a pharmaceutical company or with its authority. No breach of the Code was ruled.

This case concerned an offer by a wholesaler, Farillon Limited, in association with sales of Zeneca Pharma's product Zoladex LA.

The material provided by the complainant was a four page leaflet. The first page gave details of offers in relation to sales of Zoladex LA. Pages two and three were a price list of a large number of items and the fourth page listed a number of "best buy" products giving prices and other details including the profit for the practice.

The first page of the leaflet was headed "Zoladex LA Prize Draw" and stated "We wish to sell more Zoladex LA and in order to encourage G.P. practices to convert suitable patients from Zoladex to Zoladex LA we have arranged for a quarterly prize draw". Zoladex outer cardboard cartons were to be stamped with the GP's details and returned to the company to be used as entries in the prize draw. The first prize was a cheque for £1000. The second prize was Marks & Spencer vouchers to the value of £100 and the third prize Marks & Spencer vouchers to the value of £50.

The page also stated that "In addition any practice initiating a standing order for Zoladex LA will be sent a free bottle of wine".

COMPLAINT

A general practitioner alleged that the promotion was offensive. Breaches of Clauses 2 and 18.2 of the Code were alleged.

The complainant queried whether Farillon was a member of the ABPI or bound by its rulings. The complainant suspected that Zeneca was a member of the ABPI and was at least associated with the advertisement as it promoted its products.

RESPONSE

Zeneca pointed out that Farillon Limited was a wholesale dealer company. It was an independent company which was wholly distinct, separate and unconnected to the Zeneca group of companies. Zeneca had no involvement whatsoever in Farillon's promotion of Zoladex LA.

Zeneca first became aware of Farillon's promotion of Zoladex LA in mid 1996. It was brought to Zeneca's attention by a general practitioner. Zeneca took the view that this form of promotion was inappropriate and following representations to Farillon the promotion was stopped. Zeneca provided a copy of the letter it had sent to the general practitioner.

Zeneca submitted that it took appropriate action at the time of being made aware of the promotional activity and the action taken, contrary to bringing the industry into disrepute, exemplified the high standard of ethical behaviour demanded of the pharmaceutical industry.

On receiving notification of the complaint to the Authority, Zeneca contacted Farillon which confirmed that it had stopped the Zoladex LA promotion last year in accordance with Zeneca's request but as a result of increasing commerical pressure from competitors, Farillon had reintroduced the Zoladex LA promotion. The promotion was reintroduced without any reference to Zeneca. Zeneca provided a copy of a letter from Farillon confirming its submission on this point.

Zeneca emphasised that it had never been party to Farillon's promotion of Zoladex LA. Neither had the company condoned it. It had used its best endeavours to end the promotion and believed that it had been successful. Nevertheless Farillon was an independent company and Zeneca could not be held accountable for its actions.

PANEL RULING

The Panel noted that Clause 1.2 of the Code defined the term "promotion" as any activity undertaken by a pharmaceutical company or with its authority which promoted the prescription, supply, sale or administration of its medicines.

The Panel noted that Zeneca was not involved with the Zoladex LA prize draw and that Zeneca had contacted Farillon to try to stop the promotion.

The Panel was concerned about both the prize draw and the free bottle of wine offer. The Panel noted, however, that Farillon was a wholesaler and was not related in any way to Zeneca. The Code applied to pharmaceutical companies but not to wholesalers.

The Panel considered that the Zoladex LA prize draw did not come within the scope of the Code as it was not an activity undertaken by a pharmaceutical company or with its authority. The Panel therefore ruled no breach of the Code.

Complaint received 5 February 1997

Case completed 12 March 1997

CASE AUTH/497/2/97

HOSPITAL PHARMACIST v LILLY

Conduct of a representative

A hospital pharmacist complained about the conduct of a representative from Eli Lilly. It had been reported to the complainant that the representative had said at a group meeting that a competitor product had been withdrawn on the grounds of patient safety. The complainant had confirmed with the competitor company that this information was incorrect.

The Panel noted that the it was untrue to say that the competitor product had been withdrawn from the market on the grounds of patient safety. Although the representative had tried the next day to correct the false impression he had given about the competitor product, the Panel ruled that he had not maintained a high standard of ethical conduct and had failed to comply with all the relevant clauses of the Code.

COMPLAINT

A hospital pharmacist complained about an Eli Lilly medical representative who had held a meeting at the local community mental health centre. The community psychiatric nurse manager reported to the complainant that the representative had told staff at that meeting that a competitor product had been withdrawn from use because of 23 deaths. Naturally this statement had caused concern as community staff were aware of a number of patients currently prescribed the medicine.

In response to a phone call from the community unit, pharmacy had confirmed with the competitor company that this information was totally incorrect.

The complainant expressed concern that a medical representative could behave in such an irresponsible manner and fabricate information.

RESPONSE

Lilly submitted that the representative had conducted a group meeting regarding the recently introduced product olanzapine. During the meeting one of the community psychiatric nurses had informed the representative that a psychiatrist at a local hospital had increased the dose of a competitor product in one of her patients the previous day. In response, the representative had expressed his surprise as he was certain that the product had been withdrawn from the market due to cardiovascular side effects. The representative had then said that he would contact head office for confirmation (which he did) and that he would get back to the nurse with the correct information. He had received a response the next day confirming that the competitor product had not been withdrawn from the market and had attempted to contact the nurse with the true situation but had been unable to do so. He had therefore left messages with two other people in the same unit who said that they would pass on the message.

Lilly added that the representative had been employed by the company since March 1996 and had passed the ABPI medical representatives examination with distinction in November 1996. Early in 1997 the representative had attended an internal training course for psychotic illnesses and the use of olanzapine during which the history of the competitor product, its current status and Lilly's position was covered. Representatives had received repeated instructions that, should the competitor product be raised by customers, it was not their place to comment on the situation. Further, they had been instructed not to raise the subject in conversation with customers. Lilly was confident that representatives followed these instructions and therefore regretted the action of the representative concerned which was clearly incorrect and not consistent with his briefing.

Lilly submitted that this careless action was out of character for the representative. He was immediately apologetic and regretted the extreme inconvenience and confusion caused. His management had reinforced with him the importance of being fully aware of and compliant with company guidelines and no further disciplinary action was being considered. The opportunity to reinforce the company position had again been taken with all representatives.

Lilly contended that the representative had however commented that he had made no reference to deaths associated with the use of the competitor product. During the meeting, there was also a discussion on the use of antidepressants during which there was mention of reports of deaths (including numbers) with these products. The representative could only assume that there might have been some confusion regarding this discussion and the discussion on the competitor product.

Lilly considered that it went to great lengths to adequately train its representatives and very much regretted the occurrence of this incident and the inconvenience caused.

PANEL RULING

The Panel noted that when considering cases such as the one in question it was always difficult to determine exactly what had been said by the parties involved.

The Panel considered that representatives should not make statements that they were unsure of at meetings with the intention of confirming or denying them later. Whilst the questioner might subsequently receive a corrected statement, others at the meeting would still be left with the wrong impression. It would not usually be practicable to contact everyone at a meeting in order to revise a statement.

The Panel noted that there was no dispute that the representative had said he was certain that the competitor product had been withdrawn from the market due to cardiovascular side effects. Although the representative had said that he would confirm this point, the Panel considered that it was a very strong statement which would immediately give the audience the wrong

impression of the competitor product. Withdrawal of a product on the grounds of patient safety was a relatively rare event and such information would not be received lightly. The Panel considered that the representative had given those at the meeting particularly sensitive information about a competitor which was untrue. The Panel considered that the representative had not maintained a high standard of ethical conduct and had failed to comply with all the relevant clauses of the Code. The Panel ruled a breach of Clause 15.2 of the Code.

Complaint received 10 February 1997

Case completed 10 March 1997

CASE AUTH/499/2/97 *NO BREACH OF THE CODE*

PRIMARY CARE PHARMACY CONSULTANT v ALLEN & HANBURYS

Serevent advertisement

A primary care pharmacy consultant complained about a Serevent journal advertisement issued by Glaxo Wellcome. The advertisement also mentioned beclomethasone and fluticasone. The complainant queried why the prescribing information had not been given for all the presentations of the products mentioned.

The Panel noted that the advertisement was primarily promoting Serevent and the appropriate prescribing information had been provided. The advertisement also mentioned beclomethasone and fluticasone in general, giving specific information relating only to dosage. No mention was made of the device for administration. The Panel considered that the company was only obliged to provide prescribing information for an appropriate presentation of each of the products at the doses mentioned in the advertisement. This had been done. The Panel therefore ruled no breach of the Code.

This case concerned an advertisement for Serevent (salmeterol) which appeared in the British Medical Journal, 8 February 1997. The advertisement referred to the revised British Guidelines on Asthma Management and as well as promoting Serevent it also mentioned beclomethasone dipropionate and fluticasone propionate.

COMPLAINT

A primary care pharmacy consultant pointed out that the advertisement provided product information only about certain presentations of the products referred to in the main text, yet was of a size not covered by the abbreviated advertisement rules. Reference was made to inhaled aerosol formulations of Becotide and Becloforte but no mention was made of the same type of formulations for Serevent or Flixotide. Similarly, no reference was made to dry powder formulations of Becotide. Reference was only made to one strength of Flixotide Accuhaler when four were available.

The complainant said that the advertisement appeared to be unusual and perplexing given that those prescribing for patients who currently received their therapy through a Volumatic might be mistakenly led to believe that the aerosol form did not exist. The complainant also pointed out that to achieve the maximum dose of Flixotide quoted in the prescribing information, twenty puffs twice a day would be required meaning the device would last for three doses (one and a half days).

The complainant asked for an explanation as to why the company had not listed all the presentations of the molecules referred to together with their pack sizes and cost.

RESPONSE

Glaxo Wellcome said that the advertisement was primarily intended to highlight the fact that the revised British Guidelines on Asthma Management now recommended considering the introduction of salmeterol (Serevent) at Step 3 rather than at Step 4 as in the 1993 version. The advertisement clearly promoted Serevent and complied with all the requirements of Clause 4 with regard to this product.

The Guidelines, in the Steps referred to in the advertisement, did in addition mention generically other products and since Glaxo Wellcome had branded versions of these products, it had complied with Clause 4 of the Code for the products mentioned, beclomethasone dipropionate (Becotide and Becloforte) and fluticasone propionate (Flixotide). Further, the advertisement did not refer to any particular device or presentation of salmeterol, beclomethasone or fluticasone.

Glaxo Wellcome pointed out that the prescribing information referred to all four presentations of the Flixotide Accuhaler, 50mg, 100mg, 250mg and 500mg giving the cost of each.

Glaxo Wellcome did not accept that anyone reading the advertisement for the dry-powder formulation of Serevent which did not contain prescribing information for Flixotide Inhaler would infer that the Flixotide Inhaler had been withdrawn.

PANEL RULING

The Panel noted that the advertisement was not an abbreviated advertisement as it contained too much information and was too large to comply with the requirements for abbreviated advertisements. The advertisement was primarily promoting Serevent and prescribing information for Serevent had been provided as required by Clause 4.1 of the Code.

The advertisement also mentioned beclomethasone

dipropionate and fluticasone propionate. It was therefore necessary to include the prescribing information for these products. The advertisement referred to the products in general, giving specific information relating only to dosage. No mention was made of the device for administration. The Panel considered that the company was only obliged to provide prescribing information for the appropriate presentations for the doses mentioned in the advertisement which were beclomethasone 200 - 800mcg daily and fluticasone 100 - 400mcg daily. This had been done. There was no need to mention every presentation. The Panel therefore ruled no breach of Clause 4.1 of the Code.

Complaint received **24 February 1997**

Case completed **25 March 1997**

CODE OF PRACTICE REVIEW - MAY 1997

Cases in which a breach of the Code was ruled are indexed in **bold** type.

472/10/96	**Searle v Asta Medica**	**Promotion of Zamadol**	**Breach 7.2, 7.7 & 7.8**	**Appeal by respondent**
473/10/96	Chair, Research Ethics Committee v Solvay	Physiotens study	No breach	No appeal
475/11/96	Ciba v Searle	Arthrotec 75 journal outsert	No breach	No appeal
476/11/96	**Pasteur Mérieux MSD v SmithKline Beecham**	**Havrix mailing**	**Breach 4.1, 7.2, 7.8 & 8.1**	**Appeal by respondent**
477/11/96	**Consultant Physician v Reckitt & Colman**	**Fybozest advertisement**	**Breach 7.3 & 7.4**	**Appeal by complainant**
478/11/96	**Anon v Pfizer**	**Hospitality for a consultant**	**Breach 19**	**Appeal by respondent**
479/12/96	**SmithKline Beecham v Bayer**	**Promotion of Ciproxin**	**Breach 7.2 & 7.3**	**Appeal by respondent**
480/12/96	**Evans v Aurum**	**Promotion of adrenaline injection**	**Breach 4.1**	**Appeals by both complainant & respondent**
482/12/96	**Glaxo Wellcome v Astra**	**Booklet on inhaled corticosteroids**	**Breach 7.2**	**No appeal**
483/12/96	**Glaxo Wellcome v SmithKline Beecham**	**Promotion of Vectavir Cold Sore Cream**	**Breach 7.2, 7.4 & 20.2**	**No appeal**
484/12/96	**Napp v Sanofi Winthrop**	**Promotion of Morcap SR**	**Breach 7.2**	**No appeal**
487/1/97	Director of Primary Care Medicine v Geigy	Voltarol advertisement	No breach	No appeal
489/1/97	Anon v Bayer	Ciproxin advertisement	No breach	No appeal
490/1/97	Hospital Information Pharmacist v Parke Davis	Letter offering samples	No breach	No appeal
491/1/97	**GP v Astra**	**Use of a gift to gain an interview**	**Breach 15.3**	**No appeal**
494/1/97 & 495/1/97	**Pharmaceutical Adviser v Astra**	**Letters announcing Entocort Enema and Naropin**	**Breach 4.1 & no breach**	**No appeal**
496/2/97	GP v Zeneca	Prize draw offer as an inducement to purchase	No breach	No appeal
497/1/97	**Hospital Pharmacist v Lilly**	**Conduct of a representative**	**Breach 15.2**	**No appeal**
499/2/97	Primary Care Pharmacist Consultant v Allen & Hanburys	Serevent advertisement	No breach	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).