PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

# QUARTERLY REVIEW OCTOBER 1994

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### Case Reports

A further set of reports of cases settled by the Prescription Medicines Code of Practice Authority (PMCPA) is included in this issue of the Review.

### New Edition of the Code of Practice for the Pharmaceutical Industry

The 1994 edition of the Code of Practice for the Pharmaceutical Industry was published as a printed document in August. Bulk supplies of copies have been sent to companies which have requested them. Further copies are available from the PMCPA.

### Mailing to General Practitioners

A mailing was sent to all general practices in the United Kingdom in August, advising them that a new Code was coming into operation on 1 September, briefly detailing the changes which had been made, and inviting them to apply for a copy of the Code on the reply paid card provided. About 11,500 mailings were sent out and over 2,600 copies of the Code have been requested and dispatched.

### The EC Directive on the Advertising of Medicinal Products for Human Use (92/28/EEC)

The Directive was implemented in the United Kingdom by regulations which came into force on 9 August 1994.

They are:

> The Medicines (Advertising) Regulations 1994 (SI 1994 No 1932)
> Copies are available from branches of HMSO price £3.70
>
> The Medicines (Monitoring of Advertising) Regulations 1994 (SI 1994 No 1933)
> Copies are available from branches of HMSO price £1.55

The first set of regulations are covered by the requirements of the Code of Practice for the Pharmaceutical Industry. The second set provide both criminal and civil remedies for contraventions and permit the health ministers, with the consent of the complainant, to pass on a complaint about the promotion of a medicine to an appropriate self-regulatory body, such as the PMCPA.

The Directive was of course implemented in the Code of Practice in January 1993.

### Data Sheet and Summaries of Product Characteristics

Clause 15.7 of the Code of Practice says that representatives must provide, or have available to provide if requested, a copy of the summary of product characteristics, or where one does

not exist, a copy of the data sheet or a document with a similar content, when initiating a discussion on a medicine. Clause 17.5 says that each sample of a medicine must be accompanied by a copy of the summary of product characteristics, or where one does not exist, a copy of the data sheet or a document with a similar content.

A number of enquiries have been received in relation to these two requirements to see if they are still valid in the light of the new regulations.

The Medicines Control Agency is shortly to consult upon the question of data sheets and summaries of product characteristics and, in due course, steps are expected to be taken to deal with the present situation where, for new products, both data sheets and summaries of product characteristics are required. Until such time as this matter is resolved, Clauses 15.7 and 17.5 remain applicable. The Code's requirements in this regard will be amended as necessary at the appropriate time.

**Abbreviated Advertisements**

Companies are reminded that the 1994 edition of the Code of Practice, which came fully into operation on 1 September, changed the requirements for abbreviated advertisements. It is now obligatory to give the legal category (ie, POM, P or GSL) and to include at least one indication.

Some abbreviated advertisements are still appearing without the inclusion of the legal category and a few do not give an indication for use. Companies must take steps to include this information in their abbreviated advertisements as a matter of urgency.

**Legibility of Prescribing Information**

Much prescribing information remains difficult to read and the supplementary information to Clause 4.1 of the 1994 Code of Practice sets out recommendations for improving clarity.

They are:

- *type size should be no smaller than 7 point*
- *lines should be no more than 100 characters in length, including spaces*
- *sufficient space should be allowed between lines to facilitate easy reading*
- *a clear style of type should be used*
- *there should be adequate contrast between the colour of the text and the background*
- *dark print on a light background is preferable*
- *emboldening headings and starting each section on a new line aids legibility*

Companies are reminded that the prescribing information in their promotional material is now expected to be broadly in line with the above recommendations. Prescribing information of questionable legibility will be taken up with the company concerned under the scrutiny procedure.

**Room Rental and Postgraduate Medical Centres**

A number of enquiries have been received from postgraduate medical centres saying that they have been told by medical representatives that the 1994 edition of the Code prevents

representatives paying them for the use of their rooms. Companies are reminded that this is not the case. The supplementary information to Clause 19.2 states that "This provision does not preclude the payment of room rental to postgraduate medical centres and the like".

**Letter to Doctors on Room Rental**

To assist medical representatives when advising doctors of the proscription of the payment of room rental, letters on PMCPA notepaper are available which they can give to doctors. Companies were offered these in Circular CODE/94/52 of 12 May 1994 and many requests have been received. Copies of the letter remain available from the PMCPA.

**Responses to Enquiries**

Clause 1.2 of the Code of Practice states, inter alia, that the term "promotion" does not include replies made in response to individual enquiries from members of the health professions and they are thus exempt from the requirements of the Code.

This exception applies only to a particular answer to a particular question. It is not an opportunity to provide wide ranging promotional information which is free from the requirements of the Code of Practice.

Responses to enquiries must be genuine personalised answers to the questions raised to be exempt from the Code under Clause 1.2. If it is intended to supply information above and beyond that, then it must be treated as promotional material, comply fully with the Code and be certified. It must not be assumed that merely because information is sent out by the medical information department rather than by the marketing department, then it is not promotional in nature.

Any information or material routinely made available to representatives to give to health professionals in answer to enquiries must comply with the Code.

Enquiries about matters not covered by the licence must be handled with care and it is advisable that they are only dealt with by the company's medical or medical information departments.

**Seminars**

PMCPA training seminars on the Code of Practice open to all take place at the Royal Society of Medicine on:

Wednesday, 26 October 1994 (fully booked)
Thursday, 8 December 1994 (fully booked)
Monday, 23 January 1995
Monday, 27 February 1995
Monday, 20 March 1995

Seminars can also be arranged for individual companies.

Please ask Emer O' Reilly for details.

## Syndicate Leaders

Volunteers are sought to act on an occasional basis as syndicate leaders at the PMCPA seminars on the Code which are held at The Royal Society of Medicine in London.

There is no financial reward (though appropriate hospitality is provided!) but those taking on the role find it worthwhile and consider that it assists them in widening their own knowledge of the Code.

If interested, please contact Heather Simmonds.

# CASE REPORTS
# OCTOBER 1994

*In each case where a breach of the Code was ruled the company concerned gave an undertaking that the practice in question would cease forthwith and that all possible steps would be taken to avoid a similar breach in the future. An undertaking must be accompanied by details of the actions taken to implement that undertaking. The reports refer to the Eighth Edition of the Code, 1 January 1993.*

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CASE AUTH/89/11/93

ASTRA PHARMACEUTICALS V ALLEN & HANBURYS

"Dear Nurse" letter on Diskhalers

Astra Pharmaceuticals Ltd complained about a "Dear Nurse" letter (ref HM1014-CP/May 1993) on Diskhalers sent by Allen & Hanburys Limited. The letter was headed "Protection from Humidity" and referred to children. Astra alleged that the letter made disparaging references to its product in breach of Clause 8.1 of the Code.

There were three allegations which were considered as follows:

1. **"For example, if moisture penetrates the (terbutaline) multi-dose reservoir powder device (RPD), it may cause 'clumping' of drug particles".**

*Complaint* Astra alleged that the above claim was inaccurate and a misrepresentation of the words used in the paper to which it was referenced. The company stated that the full text was "Terbutaline sulphate is not hygroscopic. However, the aggregates formed by spheronization will harden on the surface when exposed to moisture". This in no way suggested that moisture might cause clumping of drug particles.

Astra pointed out that the reference described the precautions taken with the Turbohaler to prevent moisture penetration which included a desiccant stored in the operating unit of the inhaler. If the Turbohaler was stored for 2 years according to instructions, sufficient drying capacity of the desiccant remained for opening and closing it at least 200 times under extreme conditions.

*Response* Allen & Hanburys submitted that Astra was guilty of selective quotation as the relevant part of Wetterlin's paper read: "...the aggregates formed by spheronization will harden on the surface when exposed to moisture. This will influence the dosing characteristics and the ability of aggregates to break up into primary particles at inhalation". In other words, when moisture penetrated the device, soft aggregates would be converted into hard aggregates which would be more difficult to break up and this would influence the dose delivered. The company submitted that the word "clumping" accurately described the process in a readily understood way.

Allen & Hanburys submitted that precautions taken to protect the substance from moisture were irrelevant to the claim in question.

*Panel Ruling* The Code of Practice Panel noted that the claim stated that moisture may cause "clumping" of particles, whereas the referenced paper did not state that moisture caused aggregates to form but that aggregates would harden when exposed to moisture which would influence the dosing characteristics and the ability of aggregates to break up into primary particles. This effect was not what would generally be understood by the term "clumping". The Panel considered that a claim for which a reference was given should reflect that reference accurately. The Panel decided that the claim was misleading as it was not an accurate reflection of the paper. It therefore ruled a breach of Clause 7.2 of the Code.

2. **"If a patient accidentally breathes out through the (terbutaline) RPD prior to inhalation, more than one dose may be affected by moisture".**

*Complaint* Astra alleged that the above claim, referenced to a published but unrefereed abstract, was incorrect as the author did not study the effect of a patient accidentally breathing out through the inhaler, but simulated this in an undefined manner. The study made no use of children, who were incapable of exhaling as forcefully as adults. The authors stated that after exhaling through the Turbohaler, 20% or less of the next dose loaded was available as respirable particles, which the company alleged had no clinical relevance, since the effect of terbutaline from the Turbohaler was maintained if the respirable fraction was greater than 30 mcg, in other words 6% of the total dose of 500 mcg. Data from the referenced *in vitro* study could not be extrapolated to the clinical situation since it had no direct relevance or significance.

*Response* Allen & Hanburys submitted that the abstract had been published in a peer review journal and some of the findings had been published in more detail in another peer review journal. It was untrue to say that the authors did not study the effect of a patient accidentally breathing out through the inhaler but simulated it in a undefined manner. The abstract and the full report made it clear that the effect of actual exhalation into the device was studied. The company submitted that its claim was conservative, as the abstract stated recovery to normal values took up to 4 hours.

The company also provided a copy of a letter published in the Medical Journal of Australia which described five children whose asthma control deteriorated after changing their inhaler to the reservoir powder device (RPD).

The company referred to a previous case (Case AUTH/23/3/93) in which the Panel had decided that there was evidence to support the suggestion that more than one dose in the RPD could be affected by accidental inhalation.

*Panel Ruling* The Code of Practice Panel noted its decision in Case AUTH/23/3/93 in which it had considered there was some evidence to support the inference that more than one dose could be affected with the RPD and had ruled no breach of the Code.

The Panel decided that there was some evidence in the present case that more than one dose in the RPD might be affected by moisture if a patient accidentally breathed into the device prior to inhalation. The Panel ruled that there was no breach of the Code.

*Appeal* Astra appealed the Panel's ruling. The company maintained that data from *in vitro* studies could not be extrapolated to the clinical situation where there was no data to show that it was of direct relevance or significance. The abstract in question reported that after

exhaling through the Turbohaler, 20% or less of the next terbutaline dose loaded was available as respirable particles. The company had provided evidence that this observation had no clinical relevance since the effect of terbutaline from the Turbohaler was maintained if the respirable fraction was greater than 6%.

Astra referred to another paper as further support that *in vitro* data was not clinically relevant. The paper explained why the twin impinger which used a single constant flow rate bore no relation to patients' inhalation profiles and could not be used to predict changes in clinical efficacy.

Astra stated that the letter in the Medical Journal of Australia cited by Allen & Hanburys anecdotally reported only five patients whose asthma control failed after changing therapy to Turbohaler because of very poor or non- existent instruction by their general practitioner. This letter was not a properly controlled clinical study. In clinical studies containing substantially larger numbers of patients than the five cited in the letter to the Medical Journal of Australia, initiating therapy with Turbohaler was not associated with deterioration of asthma control.

The company contended that the *in vitro* evidence provided by Allen & Hanburys to support its claim was not adequately supported by clinical data and that there was clear evidence of clinical relevance to refute the claim.

Astra referred to the previous case (AUTH/23/3/93) in which the Panel had decided that there was evidence to support the suggestion that more than one dose in the RPD could be affected by accidental exhalation and pointed out that the complainant was a hospital consultant and the case had not been appealed. A major factor which should have been taken into account was that the "Dear Doctor" letter at issue was relating to Becodisks and the RPD to which it was compared would have been the Pulmicort (budesonide) Turbohaler. Budesonide was insoluble and there was no evidence whatsoever that more than one dose might be affected by moisture if a patient accidentally breathed out through the Pulmicort Turbohaler prior to inhalation. It should be noted that the Turbohaler contained only budesonide or terbutaline, ie no additives, bulking agents etc. In the letter published in the Medical Journal of Australia provided by Allen & Hanburys, it was not clear which Turbohaler, Bricanyl (terbutaline) or Pulmicort, the patients were receiving. Therefore this evidence in support of the claim against the Pulmicort Turbohaler was inadmissible. Furthermore, the abstract in question referred only to experiments with terbutaline and not budesonide. The decision of the Panel in that case was therefore open to question as the full facts had not been at its disposal. The data submitted by Astra regarding the reliability of both the Bricanyl and Pulmicort Turbohaler in clinical practice was accepted by regulatory authorities worldwide when granting a product licence for these products.

Astra Provided samples of Bricanyl Turbohaler and Ventodisks.

*Appeal Response* Allen & Hanburys provided samples of both the Turbohaler and the Diskhaler device for the Appeal Board to examine. The way that the devices worked was explained to the Appeal Board.

Allen & Hanburys submitted that the Panel had already ruled in the previous case (AUTH/23/3/93) that there was evidence that more than one dose in the RPD could be affected by accidental exhalation. Astra's package insert for the Bricanyl Turbohaler included the words "The contents in the inhaler are sensitive to dampness" and "Do not breathe out through the inhaler". An article stated that "If a patient breathes out into the Turbohaler before inspiring, part of the dose will be blown away and moisture deposited on the mouthpiece may partly impede deaggregation if the next dose is taken immediately", i.e. at least two doses were affected. The company considered that its statement which was the subject of Astra's appeal was supported by Astra's own promotional material and was incontrovertible.

Allen & Hanburys pointed out that Case AUTH/23/3/93 had been resolved in its favour. Case AUTH/23/3/93 related to the Pulmicort Turbohaler and not the Bricanyl Turbohaler and hence the arguments put forward by Astra in this respect were not relevant to the current case.

Allen & Hanburys said that Astra maintained that data from *in vitro* studies could not be extrapolated to the clinical situation where there were no data to show that it was of direct relevance or significance. However, the data quoted by Allen & Hanburys were clinically based: the effect of an actual exhalation into the RPD (not a simulation as claimed by Astra) was studied. After exhalation into the device, the respirable fraction of subsequent doses was reduced to 20% or less. Astra contended that this was of no clinical relevance since the effect of terbutaline from a Turbohaler was maintained if the respirable fraction was greater than 6%. However, Allen & Hanburys submitted that no data had been made available to support this anecdotal statement which had been made in an article in an Astra-sponsored, non-peer-reviewed publication.

In contrast, Allen & Hanburys cited a fully documented clinical study showing that slow exhalation into the terbutaline RPD prior to inhalation substantially reduced the bronchodilator effect. This study was published in a peer-reviewed Journal. In support of this finding the company maintained that it was well established that the respirable fraction from a dry powder inhaler decreased with decreasing flow rates and that the bronchodilator efficacy also fell at lower flow rates, suggesting that a reduction in respirable fraction indeed led to a poorer clinical response.

Allen & Hanburys submitted that since its own statement was supported by clinical data, the report provided by Astra to support its contention that *in vitro* data were not clinically relevant was itself irrelevant. Existing *in vitro* apparatus could never completely mimic the individual patient situation. Nonetheless, twin impinger data had been shown to correlate well with clinical differences in bronchodilator effect and were currently accepted as the British Pharmacopoeial standard for the evaluation of inhaler devices.

The company submitted that irrespective of the value of *in vitro* experiments what was clearly of importance was the effect on the patient. The letter in the Medical Journal of Australia was disparaged by Astra on the grounds that it was "anecdotal". Allen & Hanburys submitted that it was a detailed case report of five children whose asthma worsened on being changed from their previous device to the Turbohaler, apparently as a result of moisture penetration following washing the mouthpiece in water or breathing in and out of the device. The author specifically stated that "The moisture caused the powder to be trapped and quickly block the fine orifice in the Turbohaler". The report was anecdotal only in the sense that it did not represent the results of a controlled clinical trial. Astra claimed that two studies with larger numbers of patients had not found that the initiation of Turbohaler therapy was associated with deterioration of asthma control. However, these studies reported only the mean values of the assessments made; hence there was no guarantee that some of the subjects did not deteriorate as a result of their change of therapy.

In summary, Allen & Hanbury's position was that its statement that "If a patient accidentally breathes out through the (terbutaline) RPD prior to inhalation, more than one dose may be affected by moisture", was a plain statement of fact, supported by scientific data.

*Appeal Board Ruling* The Appeal Board noted that the complaint concerned a complex matter involving the mechanics of drug delivery. The Appeal Board considered that on balance there was sufficient evidence to support the claim that "If a patient accidentally breathes out through the (terbutaline) RPD prior to inhalation, more than one dose may be affected by moisture" and ruled no breach of the Code. The Appeal therefore failed.

3. **"The Diskhaler device with its effective protection against moisture".**

*Complaint* Astra alleged that the above claim was incorrect, as breathing out through the Diskhaler device could produce condensation, which might in turn lead to coating of the internal surface with powder from the next inhaled dose. Unlike the Turbohaler, the Diskhaler had no seal to protect against moisture penetration and no mechanism for recovery from exposure.

*Response* Allen & Hanburys submitted that Astra had quoted selectively. The letter stated "With the Diskhaler device the drug particles are protected against moisture in hermetically sealed blisters as shown in this diagram. I hope that the Diskhaler device, with its effective protection against moisture, proves useful for the asthmatic children in your care". The protection clearly referred to the drug particles which were indeed hermetically sealed and moisture resistant.

The company submitted that the suggestion that breathing into the Diskhaler could produce condensation, which might lead to coating of internal surfaces with powder from the next dose, was purely speculative. The company had no data to suggest that this could occur. All parts of the Diskhaler were accessible for cleaning and a brush was provided within the Diskhaler casing for cleaning. Examples of the disks were provided.

*Panel Ruling* The Panel considered that there was no evidence to support the allegation which had been made and therefore ruled no breach of the Code.

*Appeal* Astra appealed the Panel's ruling. The company pointed out that Allen & Hanburys stated in its own promotional material that "Only one dose may be affected by moisture if the patient accidentally breathes into the Diskhaler". Therefore, clearly the device could not be claimed to have effective protection against moisture if even one dose could be affected. Furthermore, the Diskhaler device had a grid exposed on one side to saliva and exhaled air. On the underside, the grid was exposed to the powder. The powder side of the grid could not be cleaned with the brush provided unless the disk was removed and the device was dismantled.

Astra drew particular attention to the inhalation channels of both devices. The Turbohaler device contained a spiral arrangement in the mouthpiece which caused turbulence and deaggregation of particles as a patient inhaled. This prevented clumping of particles, even if a patient breathed into the device prior to a subsequent inhalation. No such mechanism existed with the Diskhaler device. The Turbohaler also contained a dessicant to protect the drug in the reservoir. The disks might be hermetically sealed but since they might be prescribed separately as refills, it was misleading to ascribe this property to the Diskhaler device.

*Appeal Response* Allen & Hanburys submitted that the protection against moisture was clearly being ascribed to the Diskhaler system as a whole. The disks were an integral part of the system and the Diskhaler was not available as a separate item. The system embodied a mechanism for recovery from exposure in that all parts were accessible for cleaning and drying as required. Astra was incorrect in stating that the powder side of the grid could not be cleaned unless the disk was removed and the device dismantled. The powder side of the grid was easily accessible with the cleaning brush included without dismantling the device; this was however a simple manoeuvre in any case. The company could not see how the spiral arrangement in the mouthpiece of the Turbohaler could prevent clumping of the particles. Indeed, by trapping moisture it might enhance the hardening of the existing drug aggregates. It was not possible for patients to gain access to these spiral channels in order to clean them. The inclusion of a dessicant seemed to be irrelevant, since it had clearly been shown not always to be effective in preventing interference by moisture with more than one dose of the medicine.

In conclusion, the company submitted that it had provided clinical evidence that drug delivery from the Turbohaler could be impaired by moisture with clinical consequences. It had no evidence that this could happen or had ever happened with the Diskhaler and Astra had failed to provide any such data in support of its appeal. Unlike the Turbohaler device, the medication in the Diskhaler device was contained in individual hermetically sealed moisture-proof blisters, which were inaccessible until pierced immediately prior to inhalation. Hence the company maintained that its dosing device was indeed designed to provide effective protection against moisture.

*Appeal Board Ruling* The Appeal Board considered that there was no evidence to support the allegation which had been made and ruled no breach of the Code. The Appeal therefore failed.

**Complaint received** **5 November 1993**

**Case completed** **23 February 1994**

CASE AUTH/97/1/94

CONSULTANT PHYSICIAN V MEMBER COMPANY

Prelaunch promotion

*Complaint* A consultant physician complained that a brochure sent as part of a prelaunch mailing by a member company was not accompanied by a data sheet and that a particular statement in it regarding another company's product was not a balanced reflection of the evidence. The complainant also queried the overall thrust of the promotion which appeared to be that the new product (when launched) would be more efficacious than the competitor.

The allegation concerning the absence of the data sheet was taken as concerning the absence of prescribing information as the provision of a data sheet for a new product was not a requirement of the Code.

*Company Response* The company stated that the aim of the mailing was to draw doctors' attention to the company's expertise in the area and to provide what was intended as a useful brief guide to one particular disease area and its treatment. The mailing did not specifically mention its new product.

*Initial Ruling by the Panel* The Panel noted that the mailing in question, although it referred to a group of medicines, did not specifically mention the respondent company's product by either brand or generic name. The Panel did not consider that general practitioners receiving the mailing would have associated the message in it with any particular product as, at that time, the company's product had not been launched. The Panel therefore ruled that the item was not promotional and did not come within the scope of the code.

*Appeal by Complainant* The complainant did not accept the company's submission and alleged that, with the benefit of hindsight, it was clear that the company was preparing a platform for the launch of its new product.

The company reiterated its submission to the Code of Practice Appeal Board at the appeal.

*Appeal Board Ruling* The Appeal Board considered that just because the name of the medicine was not mentioned in material, this did not automatically mean that it was outside the Code. The booklet at issue was clearly part of the prelaunch campaign for the product as it discussed limitations in the then existing treatment for the disease area and outlined what was described in the booklet as "the treatment need". The booklet also contained a prominent strap line referring to working towards a new treatment for the particular disease. The Appeal Board decided that the booklet was a promotional item coming within the definition of the Code and therefore overturned the ruling made by the Panel.

The case was referred back to the Code of Practice Panel for it to consider the actual matters of complaint.

*Panel's Further Rulings* Firstly, the Panel considered the Appeal Board ruling that the booklet was a promotional item coming within the definition of promotion in the Code. The Panel considered that the item was promotional in the general sense as forming part of a promotional campaign for a product. The requirements of the Code with regard to accuracy, balance, taste etc therefore applied. The booklet clearly set the scene for the promotion of the product when launched but it was not in itself a specific advertisement for the product. It could not be described as promotion of a medicine prior to the grant of a licence nor was the prescribing information for the product required. The Panel therefore ruled there had been no breach of the Code in regard to the absence of prescribing information. Neither did the Panel consider that a data sheet was required, although this was not a matter for the Panel to determine.

The Panel did not accept that the disputed statement in the booklet was unacceptable and ruled no breach of the Code in that regard. Finally, the Panel did not accept the complainant's allegations that the whole thrust of the promotion was that the new product was more efficacious than the competitor. The new product was not actually mentioned in the mailing and no comparative claims were made. No breach was ruled.

**Complaint received** **5 January 1994**

**Case completed** **25 May 1994**

CASE AUTH/100/1/94

ALLEN & HANBURYS V ASTRA

**Promotion of Turbohaler**

Allen & Hanburys Limited complained about a detail aid and a "Dear Doctor" letter (Ref TUR B93879) issued by Astra Pharmaceuticals Ltd. There were two matters of complaint which were considered as follows:-

1. Lung deposition claims

*Complaint* Allen & Hanburys drew attention to a page in a detail aid headed

"efficient delivery" which included a table headed "Deposition of inhaler devices". The table gave the percentage reaching the lungs as 27% for Turbohaler 8.7% for the MDI, 12.4% for the dry powder disc system and 20.9% for the MDI with spacer. The table was referenced to three studies.

The complainant alleged that the studies were not comparable and the data were misleading. The complainant pointed out that the data from separate studies, carried out over a nine year interval in different units using varying methods, had been presented as if they were directly comparable. The studies differed greatly in pertinent factors such as the medicine or marker substance used, subject type (patient or volunteer) and standardisation of factors critical to the optimum use of inhaler devices such as inspiratory flow rates. Furthermore, three selected studies had been presented instead of a fair representation of all the scientific evidence. The claimed lung deposition of 27% for the Turbohaler did not reflect the balance of evidence. Values of lung deposition recorded in patients included 9.1%, 14.2% and 16.8%.

The complainant drew attention to one of the studies which was used as a reference for the lung deposition of the MDI and the MDI with spacer, and employed a method which simulated poor inhaler technique. The study stated that "Less than 10% of the dose discharged from the metered dose inhaler reached the lungs because of the time delay imposed between aerosol actuation and inhalation which was intended to simulate poor inhaler technique. With good co-ordination and the same inhaled flow rate and breath holding pause about 15% of the dose would have been expected to reach the lungs". The complainant alleged that the conclusions had been ignored in order to create a misleading impression of poor deposition from the MDI.

The complainant alleged the selected use and misrepresentation of data was in breach of Clause 7.2 of the Code.

*Response* Astra Pharmaceuticals Ltd submitted that it had made no claims for clinically relevant superiority in lung deposition using the Turbohaler device. The page in question dealt with delivery systems and gave lung deposition values for the commonly used delivery systems. No claim concerning clinical efficacy was made. The company submitted that the conclusion which could reasonably be drawn from the data was that more lung deposition took place with the Turbohaler than with a metered-dose inhaler. The company submitted that one of the references quoted, reviewed and referred to 180 publications as well as providing experimental values for 65 subjects. The company submitted that it had been careful to differentiate between studies on healthy volunteers and those on patients.

*Panel Ruling* The Panel noted that some of the data presented were from healthy volunteers and some were from patients. It was not immediately clear which studies were on healthy volunteers due to the page layout. It further noted that the results for the MDI and MDI with spacer came from a study which was designed to simulate poor inhaler technique and in this study the pressurised aerosol deposition was measured by incorporating teflon particles. The Panel also noted the studies provided by the complainant which gave values of lung deposition recorded for Turbohaler in patients of 9.1%, 14.2% and 16.8%. It considered that the figure of 27% given in the chart was not a fair reflection of all the available evidence.

The Panel considered that the studies were not directly comparable and that the table did not reflect the balance of evidence. The Panel therefore ruled a breach of Clause 7.2 of the Code.

*Appeal* Astra appealed this ruling. Astra referred to the study which had been used as a reference for the lung deposition of the MDI and the MDI and spacer, and drew attention to the statement in the study report cited by Allen & Hanburys that "Less than 10% of the dose discharge from the metered dose inhaler reached the lungs because of the time delay imposed

between aerosol actuation and inhalation, which was intended to simulate poor inhaler technique. With good co-ordination the same inhaled flow rate and breath holding pause about 15% of the dose would have been expected to reach the lungs". Astra pointed out that the 15% figure was referenced to a second study by the same author where aerosol deposition was measured under a range of conditions. These simulated perfect technique in a way which was unrepresentative of the real clinical situation. Patients inhaled through apparatus which limited their inhalation flows to preset values, measured inhaled volumes and automatically fired the aerosol at predetermined settings. The optimum conditions included an inhalation flow through the MDI of 30 litres per minute subsequent breath holding for 10 seconds and firing the aerosol during early inspiration. When patients inhaled at a faster flow rate lung deposition was in the range of 6-9% depending on the inhaled lung volume. A recent study found that the mean inspiratory flow rate at the instant of aerosol actuation was 142 litres per minute and that 75% of patients inhaled at greater than 80 litres per minute. The study concluded that "In a specialist asthma clinic, the majority of patients in the study used pressurised aerosols ineffectively despite repeated tuition". Further problems caused by poor co-ordination have long been known and a recent audit of patients being treated in general practice found that only 45% of patients had good MDI technique.

The company referred to a summary of studies on lung deposition from MDIs using all techniques and submitted that the largest number of mean observations (observations being defined as the results from a particular study not from a particular patient) fell within the 5-9.9% range of total lung deposition. Similar results were obtained for observations in studies using the same method of measuring.

The company submitted that a summary of studies on the Turbohaler gave the largest number of mean observations within the range 25-30% lung deposition. The figures provided by Allen & Hanburys of 9.1%, 14.2% and 16.8% were taken from two studies published in 1989 and 1991 respectively. Astra submitted that more recent studies using improved methodology showed lung deposition values from the Turbohaler of 27% up to 32%. The claim in the detail aid of 27% lung deposition with Turbohaler was supported by data from at least three up-to-date studies and could be considered to be a fair reflection of all the available recent scientific evidence in a field which was advancing.

The company submitted that total lung deposition was similar in patients and healthy volunteers. Three studies had been carried out using a variety of inhalers and these had found no difference in percentage lung deposition between patients and healthy volunteers. The company submitted that the relevance of data derived from healthy volunteers was therefore established.

The company submitted that it was impossible to radio label most beta agonists or steroids with a suitable gamma emitter so other methods were required such as using radioactive teflon particles as had been done in the study quoted in the table. Teflon particles were the same size as those of the medicine. Another technique was used for the Turbohaler.

*Appeal Board ruling* The Appeal Board noted that one of the studies submitted by Astra stated that the lung deposition of budesonide from the Turbohaler was twice that from the pressurised MDI.

The Appeal Board considered that the table gave the impression that it was a comparison of different delivery systems using the same basis and same product but this was not so. In this regard it noted that the figures for the MDI and MDI with spacer were obtained from studies using teflon particles, whereas the figure for the Turbohaler was for a terbutaline Turbohaler and the figure for the dry powder disc system was for salbutamol. The Appeal Board was also concerned that the figures for the MDI and the MDI with spacer were from a study designed to simulate poor inhaler technique. Prescribers would assume that the deposition values related to the correct use of the MDI.

The Appeal Board was also concerned that the table was not clear in distinguishing studies done on patients from those done on healthy subjects. It noted the evidence submitted by Astra that there was no difference in lung deposition in healthy volunteers to that in patients but considered that in any event it should have been made immediately clear to the reader that some of the studies were on healthy volunteers.

Overall the Appeal Board considered that the studies were not directly comparable, there was not sufficient information given as to the basis of the comparison and the table did not reflect the balance of the evidence. The Appeal Board ruled a breach of Clause 7.2 of the Code. The appeal therefore failed.

2. Clinical Studies

*Complaint* Allen & Hanburys drew attention to a "Dear Doctor" letter which stated that a dose reduction was possible when transferring patients from a beclomethasone dipropionate MDI to budesonide Turbohaler. The complainant alleged that claims for a dose reduction could not be substantiated by the available scientific data. Nor did the claims represent all the available evidence.

The "Dear Doctor" letter reported on an open parallel group study involving 146 patients in which the group receiving Pulmicort Turbohaler required significantly less inhaled steroid than the beclomethasone dipropionate (MDI) group to maintain equivalent efficacy. The results of the study were also shown in a graph.

The complainant pointed out that the difference was 0.9 of a puff less in the budesonide group (4.5 ± 2.1) compared with the beclomethasone dipropionate group (5.4 ± 2.0). Although this was claimed to be statistically significant ($P < 0.01$), this was questionable since the error bars appeared to extend over twice the difference claimed between the two devices.

The complainant stated that the balance of available data did not suggest that there was a difference between beclomethasone dipropionate and budesonide. It was generally accepted that the products were equipotent dose for dose regardless of delivery device. Allen & Hanburys stated that the scientific evidence confirmed this view. Further, the British Thoracic Society agreed to recommend 200-800mcg daily of either beclomethasone dipropionate or budesonide as initial prophylaxis of adult asthma, regarding them as clinically equivalent.

The complainant referred to two previous rulings of the Code of Practice Committee (COP/1141/9/92 and COP/1144/10/92) in which the Committee had accepted that the balance of scientific evidence showed no difference between these two inhaled corticosteroids.

The complainant was also concerned that a quotation in the letter "When patients are switched from pMDI to Turbohaler, this is an excellent opportunity for reduction in inhaled steroid dose, and attempts should be made to reduce the inhaled steroid dosage to the minimum possible level, in accordance with the "step-down" recommendation in current management guidelines" and pointed out that the first sentence of the quotation which read "Patients will commonly need a lower dose of budesonide by Turbohaler than they would by pMDI" had been omitted. The complainant alleged that the omission of the first sentence misled the reader into believing that the quotation referred to changing patients from beclomethasone dipropionate pMDI to Turbohaler because of the juxtapositioning of the quotation to the study results discussed earlier. With the inclusion of the first sentence it was evident that the quotation referred to transferring patients from the budesonide MDI to Turbohaler.

The complainant alleged that the "Dear Doctor" letter was misleading and not substantiated in breach

of Clauses 7.2 and 7.3 of the Code.

*Response* Astra Pharmaceuticals Ltd stated that the mailing accurately reported the study. Astra also drew attention to the results of dose reduction when switching from beclomethasone dipropionate MDI and spacer to budesonide Turbohaler and from budesonide Nebuhaler to budesonide Turbohaler, which concluded that the maintenance dose of inhaled steroid therapy could often be reduced without deterioration in lung function when changing patients from treatment with pMDI to budesonide Turbohaler.

Astra submitted that the quotation was accurate.

*Panel Ruling* The Panel accepted that there was some evidence in the study that the same control of asthma could be achieved with a lower amount of Pulmicort Turbohaler than with a beclomethasone dipropionate MDI but this was not in accordance with the generally accepted opinion that the products were equipotent. The Panel noted the recommendations for use of the products in the British Thoracic Society Guidelines on the management of Asthma.

The Panel considered that it was misleading to omit the sentence from the quotation, "Patients will commonly need a lower dose of budesonide by Turbohaler than they would by pMDI" which made it clear that the comparison referred to was of budesonide MDI with budesonide Turbohaler and not of budesonide Turbohaler and beclomethasone dipropionate MDI.

Overall, the Panel decided that the mailing was misleading and not of fair reflection of the available evidence. The Panel therefore ruled a breach of Clause 7.2 of the Code.

*Appeal* Astra appealed this ruling. Astra submitted that there was an emerging body of evidence which demonstrated that as might be expected from the lung deposition studies, the dose of corticosteroid needed to control asthma was lower with Turbohaler than with MDI. Astra submitted that the comments of Allen & Hanburys concerning the statistical analysis of the study were unfounded. The standard deviation of the number of puffs used by each group at the end of the study could not be used in the way Allen & Hanburys had done.

Astra submitted two further supporting studies, one which reported that it was possible to reduce the dose of budesonide by 50% when given by Turbohaler (compared with MDI enhanced with spacer). The patients had been carefully checked prior to inclusion in the study to ensure that they were not being over-treated before receiving half the dose of budesonside via the Turbohaler. Another studied 76 patients using Becotide MDI (enhanced with spacer) and when these patients were transferred to Pulmicourt Turbohaler a 37% reduction in steroid dose was possible.

Astra submitted that the issue of product equipotency had been confused with that of substance equipotency. The British Thoracic Society (BTS) guidelines stated that "Selection of inhaler devices is as important as selection of drugs..." The representatives submitted that the membership of the BTS was not asked about relative potency and further the 1992 revision of the guidelines predated almost all of the published work related to improved lung deposition with the Turbohaler.

Astra submitted that the edited quotation in the letter which had omitted the first sentence of the quotation with regard to "Patients will commonly need a lower dose of budesonide by Turbohaler than they would by pMDI" there was convincing data to show that the Turbohaler produced greater lung deposition and enabled steroid dose reduction compared with the MDI. This was true for either budesonide or beclomethasone dipropionate MDI. It was not therefore misleading to omit the first part of the quotation since the claims for dose reduction could be substantiated.

*Appeal Board Ruling* The Appeal Board accepted that the company had data to show that inhaled steroid dose could be reduced with a Turbohaler compared with an MDI. The Appeal Board accepted that the references in the "Dear Doctor" letter to reducing the dose with the Turbohaler were supported by the available evidence. The Appeal Board ruled no breach of the Code. The appeal on this aspect was therefore successful.

With regard to the edited quotation, the Appeal Board accepted that the quotation given in the "Dear Doctor" letter "When patients are switched from the pMDI to Turbohaler this is an excellent opportunity for a reduction in the inhaled steroid dose and attempts should be made to reduce the inhaled steroid dosage to the minimum possible level..." was supported by the available evidence. It considered, however, that the omission of the sentence from the quotation "Patients will commonly need a lower dose of budesonide by Turbohaler than they would by pMDI" meant that the quotation did not accurately reflect the meaning of the author and therefore ruled a breach of Clause 11.2 of the Code. The appeal on this aspect was therefore unsuccessful.

**Complaint received** **14 January 1994**

**Case completed** **16 May 1994**

CASE AUTH/116/2/94

ALLEN & HANBURYS LIMITED V MEMBER COMPANY

Claims for compatibility with device

*Complaint* Allen & Hanburys Limited complained about promotional material issued by a member company which claimed that certain of its products were compatible with a device which was clearly that of Allen & Hanburys. It was alleged that this claim was not authorised by the member company's product licences and was in breach of Clause 3.2 of the Code.

*Response* The company concerned submitted that it made no claim for clinical efficacy but *in vivo* and *in vitro* data had shown no differences in delivery of the medication. There were currently no licensing requirements for use of the products with the devices.

*Panel Ruling* The Code of Practice Panel did not accept that the company had promoted its products outside the terms of its product licence and ruled that there was no breach of Clause 3.2.

The Panel did, however, consider that the company had made a claim for clinical efficacy which was not supported by sufficient evidence and ruled that there had been a breach of Clause 7.3.

*Appeal* The company maintained that it had not made a claim for clinical efficacy but even if its claims were interpreted in that way, there was adequate supporting evidence and therefore no breach of Clause 7.3.

*Appeal Board Ruling* The Appeal Board considered that a claim had been made that the product and the device could be used together in a clinically acceptable way. The Appeal Board considered that to make such a claim it was necessary to have some evidence that there would be no

change in the expected clinical effect. There are no official guidelines at the present time though it was understood that they were under consideration. The Appeal Board considered that, in the light of present requirements, the company had submitted sufficient evidence to justify its claim. It was ruled there had been no breach of the Code. The appeal therefore succeeded.

**Complaint received** **11 February 1994**

**Case completed** **18 May 1994**

CASE AUTH/117/2/94

ALLEN & HANBURYS LIMITED V MEMBER COMPANY

Claims for compatibility with device

*Complaint* Allen & Hanburys Limited complained about promotional material issued by a member company which claimed that certain of its products were compatible with a device which was clearly that of Allen & Hanburys. It was alleged that this claim was not authorised by the member company's product licences and was in breach of Clause 3.2 of the Code.

*Response* The company concerned submitted that its products had been licensed on the basis of essential similarity to the innovator's products, in this case Allen & Hanburys'. The company was therefore justified in recommending the use of its products with the device.

*Panel Ruling* The Code of Practice Panel did not accept that the company had promoted its products outside the terms of its product licence and ruled that there was no breach of Clause 3.2.

The Panel did, however, consider that the company had made a claim for clinical efficacy which was not supported by sufficient evidence and ruled that there had been a breach of Clause 7.3.

*Appeal* The company presented data which it had produced to satisfy itself that its products' performance was satisfactory with the device. There had been no breach of Clause 7.3.

*Appeal Board Ruling* The Appeal Board considered that a claim had been made that the product and the device could be used together in a clinically acceptable way. The Appeal Board considered that to make such a claim it was necessary to have some evidence that there would be no change in the expected clinical effect. There were no official guidelines at the present time though it was understood that they were under consideration. The Appeal Board considered that, in the light of present requirements, the company had submitted sufficient evidence to justify its claim. It was ruled there had been no breach of the Code. The appeal therefore succeeded.

**Complaint received** **11 February 1994**

**Case completed** **18 May 1994**

CASE AUTH/120/2/94

BAKER NORTON V ALLEN & HANBURYS LIMITED

Compatibility of inhalers and spacers

Baker Norton, a division of Norton Healthcare Ltd, complained about claims made by Allen & Hanburys Limited in journal advertisements and in letters to health professionals about the use of the Volumatic spacer with inhalers other than Allen & Hanburys' own. There were six allegations.

1. **"Use of untested MDIs with the Volumatic could result in delivery of significantly greater or lesser amounts of drug to the patient compared with the use of Allen & Hanburys' inhalers, with the risk of over or under-treatment."**

*Panel's consideration* This claim was made in an advertisement in The Pharmaceutical Journal, 29 January 1994 and in an undated "Dear Doctor" letter and was alleged to be in breach of Clause 7.2 of the Code.

Baker Norton stated that its metered dose inhalers (MDIs) had been demonstrated to be essentially similar and bioequivalent to the brand leader products (in this case Allen & Hanburys') on the market. At no time in the last six years of Norton's salbutamol MDI being approved and marketed, and despite extensive use of salbutamol inhalers with the Volumatic, had any safety or efficacy issues been reported. The use of spacer devices with MDIs was well accepted in clinical practice and, indeed, was in line with the British Thoracic Society guidelines. The purpose of large volume spacer (LVS) devices was to aid patient coordination of actuation with inhalation and to reduce oropharyngeal deposition of the medicine.

Allen & Hanburys submitted that Baker Norton claimed that its MDIs were bioequivalent to Ventolin. There were 12 varieties of generic or branded generic salbutamol inhalers and 2 branded generic beclomethasone inhalers available currently on the UK market. Even if Baker Norton proved that its metered-dose inhalers were clinically bioequivalent to Ventolin when used with the Volumatic, this would be a specific case and would not affect the validity of Allen & Hanburys' statement "Use of untested MDIs with the Volumatic could result in delivery of significantly greater or lesser amounts of drug to the patient..."

The Code of Practice Panel had noted that the claim in question referred to the use of "untested metered-dose inhalers with the Volumatic". The Panel had considered that the claim was misleading as it was not the MDIs that were untested, as they had all received product licences, but combinations of MDIs and the Volumatic which might be untested. This had not been made clear. The Panel had therefore ruled a breach of Clause 7.2 of the Code.

This was not appealed.

2. **"Allen & Hanburys produces the Volumatic large volume spacer which is specifically designed for use with our inhalers. Allen & Hanburys' products have been licensed for use with the Volumatic device following assessment of safety and efficacy based on data submitted by us to the registration authority. To our knowledge other inhalers are not approved for use, nor have they been clinically tested successfully for use with the Volumatic device."**

*Panel's consideration* Baker Norton alleged that this claim, made in a "Dear Doctor" letter, was

misleading, as it suggested that inhalers currently had to be approved for use with large volume spacers such as the Volumatic. Spacer devices were not currently covered by regulatory requirements and if covered at all would be covered by the evolving device regulations. The fact that Allen & Hanburys' inhalers had been licensed for use with the Volumatic spacer was its own prerogative, as was the fact that it carried out clinical studies with the Volumatic: it was not a licence requirement of the MCA or any other regulatory body. As long as the inhaler itself had proven bioequivalence and fitted the spacer perfectly, there should be no safety or efficacy issue. The phrase "other inhalers are not approved for use" was grossly misleading and in breach of Clause 7.2 of the ABPI Code of Practice.

Allen & Hanburys did not agree that its statement misrepresented current regulatory practice. The company had submitted the data on the performance of its inhalers in combination with the Volumatic to the MCA, which had approved the inclusion of such use in the appropriate product licences. None of the data sheets for generic MDIs included an indication for use with large volume spacer devices and hence it was correct to state that to its knowledge other inhalers were not approved for use with the Volumatic. Baker Norton, in promoting the use of its inhalers with large volume spacers, was promoting a use which was outside the terms of its product licence.

It had not been clear to the Panel whether it was necessary for product licences to refer to spacers in order to sustain a claim that MDIs and spacers were clinically compatible. It had noted that the Volumatic did appear to have been recognised in the relevant product licences for use with Allen & Hanburys' products. It had further noted that product licences for products other than Allen & Hanburys' did not appear to cover the question of use with spacers. The Panel had considered that Allen & Hanburys was not unjustified in stating that "other inhalers are not approved for use, nor have they been clinically tested successfully for use with the Volumatic device" as in the claim at issue. The Panel had therefore ruled no breach of the Code.

*Appeal* Baker Norton said that nobody was denying that Allen & Hanburys' products had been licensed for use with the Volumatic device, although this was not a licence requirement. Allen & Hanburys' data sheets only allowed it to comment on the Volumatic improving co-ordination of patients who find using the MDIs on their own difficult. There was no reference to the use of the Volumatic in the "Dosage and Administration" section of the data sheet. This clearly indicated that dose did not require any adjustment and that individual titration when a Volumatic was used as opposed to an MDI on its own was not taken into consideration. Baker Norton made available clinical data for its own MDI with the Volumatic spacer which it said demonstrated efficacy equivalent to Allen & Hanburys' own product.

Allen & Hanburys said that the statement complained of and now the subject of appeal was factually correct. To Allen & Hanburys' knowledge other MDIs were not specifically approved for use, nor had they been clinically tested for use with the Volumatic. MDIs did not have to be approved by the MCA for use with spacer devices to receive marketing authorisation but such use clearly would need to be approved if the marketing company sought to promote use of its MDIs with specific spacers. Even if Baker Norton could produce satisfactory clinical bioequivalence evidence and get its product licences amended, there were still ten other companies marketing generic inhalers so the problems still remained.

*Appeal Board Ruling* There was some concern that the statement implied that inhalers had to be approved for use with spacers but on balance the Appeal Board decided the statement was acceptable. The Appeal Board ruled that there had been no breach of the Code of Practice. The Appeal therefore failed.

3. **"Recently, the issue of incompatibility of generic inhalers with the Volumatic has been raised."**

*Panel's Consideration* Baker Norton alleged that this claim, which had been made in a "Dear Practice Nurse" letter dated September 1993, referenced to a study by Lee G et al, did not accurately reflect the meaning of the author, in breach of Clause 11.2 of the Code. The study by Lee looked primarily at the dose delivery, physical characteristics, i.e. compatibility (physical fit), with the Volumatic and inhaler colours of the various salbutamol, MDI products available on the UK market. The conclusion drawn with regard to the Volumatic was that all except one product (no longer marketed in the UK) were physically compatible with satisfactory mouthpiece/Volumatic fit. The Lee paper was trying to make the opposite point to that inferred by Allen & Hanburys.

Allen & Hanburys drew to the Panel's attention the fact that the paper by Lee et al submitted as a reference by Baker Norton was not the reference given in its "Dear Practice Nurse" letter which was the actual subject of this section of Baker Norton's letter of complaint. The reference given in the "Dear Practice Nurse" letter was a letter by Lee published in The Pharmaceutical Journal which concerned a "Dear Hospital Pharmacist" letter. The Panel had already found in a previous case that the letter from Lee et al, while assessing the compatibility of the spacer device and metered-dose inhalers, did raise the issue of incompatibility.

The Panel had noted that this case was similar to an earlier case. In that case, the Panel had considered that it should not be assumed that any inhaler was compatible merely because the mouthpiece fitted the Volumatic and that it was for other companies to show that their generic MDIs combined with the Volumatic were clinically equivalent to the Allen & Hanburys' combination. The Panel had considered that the issue of incompatibility had been raised in the letter by Lee. The "Dear Practice Nurse" letter was therefore not misleading as alleged. The Panel had accepted the comments from Allen & Hanburys and had therefore ruled no breach of the Code.

*Appeal* Baker Norton said while understanding the Panel's view that it had already ruled in a previous case on the issue of Lee et al, it may have been at that time that the Panel did not have all the evidence available which had now been provided. Since that case studies such as the West Midlands Health Pharmacy Division report had been published. The fact that Allen & Hanburys was referencing a letter to The Pharmaceutical Journal by Lee did not preclude it from being aware of the full study by Lee et al.

Allen & Hanburys said that the statement was not misleading and that the issue had indeed been raised in the publication by Lee which it had cited. Baker Norton said however, that Allen & Hanburys should have been aware of Lee's full study results. It was. They had no bearing on the allegation. The only other point raised referred to the unpublished study by the West Midlands Health Pharmacy Division discussed in detail in the original documentation sent to the PMCPA. This was a purely *in vitro* study which used unvalidated methodology.

*Appeal Board Ruling* The Appeal Board considered that the use of the reference to Lee was misleading as that referred to spacers solely in relation to physical fit and concluded that they did fit with one exception and that one was to be modified so as to fit. The implication of the "Dear Practice Nurse" letter was that it was more than physical fit. It was ruled that there had been a breach of Clause 7.2 of the Code. The appeal therefore succeeded.

4. **"It is unclear to what extent it is permissible, from the point of view of spray kinetics, and hence adequate drug delivery, to combine any spacer with any conventional MDI."**

*Panel's consideration* Baker Norton alleged that this claim, which had been made in the "Dear Doctor" letter and the "Dear Practice Nurse" letter of September 1993, was taken out of context. The claim was referenced to a review article by Newman covering the delivery systems available for inhaled medicines. The article clearly stipulated upfront that no inhalation device was perfect. As regards MDIs, the Newman review stipulated that "the percentage of the dose reaching the lungs depends on many factors, including characteristics of the individual subject who inhales the spray, the mode of inhalation and physico-chemical factors". It concluded that "Despite the low efficiency of MDIs, full drug efficacy can be achieved with inhaled bronchodilators in doses of only a few tens or hundreds of micrograms, which demonstrates the extreme potency of these compounds".

Allen & Hanburys submitted that the claim was a direct quote from Newman's review and in recent conversation the company had confirmed that it still represented his current view. Spacer ergonomics were not designed specifically for one medicine and the performance of each inhaler should be determined for use with that spacer, as Allen & Hanburys had done.

The Panel had considered that the claim was acceptable. Generic MDIs were not licensed with regard to spray kinetics in combination with a spacer. It was clear that if the use of a spacer significantly altered delivery, the dose of the medicine could be adjusted to suit the patient. The burden of proof of compatibility lay with the company making the claim and the Panel had considered that Allen & Hanburys had demonstrated the compatibility of their MDIs with their spacer; other companies had to demonstrate that any spacer was compatible with any conventional MDI. The Panel had accepted the comments from Allen & Hanburys and therefore ruled no breach of the Code.

This was not appealed.

5. **"The issue of incompatibility of some generic inhalers with the Volumatic was recognised by the Pharmaceutical Services Negotiating Committee (PSNC), which has recently gained agreement from the Department of Health that when a prescription is written for salbutamol inhaler plus a Volumatic device, or where the patient has been instructed to use the inhaler with the Volumatic, the pharmacist can dispense a Ventolin (salbutamol) inhaler and will now be reimbursed."**

*Panel's consideration* Baker Norton stated that this claim had been made in an advertisement in The Pharmaceutical Journal, August 1993 and in the "Dear Practice Nurse" letter dated September 1993 and subsequently amended in the updated advertisement published in The Pharmaceutical Journal, 29 January 1994. It was misleading and disparaging. The updated advertisement stated:

> "The Department of Health has stated that from 1st January 1994, pharmacists who have concerns about product compatibility with the Volumatic can dispense Ventolin (salbutamol) Inhalers against prescriptions for salbutamol with (or intended for use with) a Volumatic device providing that they have obtained the prescriber's approval. The prescriber's approval having been obtained, it is not necessary to return the prescription for alteration. To ensure reimbursement the prescription should be endorsed "Ventolin" and "prescriber approved" or "PA" and initialled and dated by the pharmacist".

Baker Norton stated that the original advertisement did not reflect the true situation which was that the change could only take place after checking with the prescribing physician regarding his intention and the prescription endorsed accordingly.

Allen & Hanburys did not accept the allegation that its original advertisement in August 1993 and the "Dear Practice Nurse" letter of September 1993, did not reflect the true situation. The original ruling

made by the DOH was exactly as represented in the autumn communications. Subsequently the DOH had amended the ruling, and it immediately issued new communications to appraise healthcare professionals of the change.

The Panel had considered that the original claim and subsequent amendment reflected the advice issued by the DOH. The Panel had accepted the comments of Allen & Hanburys and therefore ruled no breach of the Code.

This was not appealed.

6. **"....proven through research. In addition Allen & Hanburys' branded products provide educational support for patients with asthma and an effective range of asthma management services for prescribers which are not usually available with generic alternatives... We ask you to bear in mind that generic products do not usually offer these support materials and services to healthcare professionals."**

*Panel's Consideration* The statement was made in the "Dear Doctor" letter and in a second "Dear Practice Nurse" letter dated November 1993.

Baker Norton alleged that the claims were in breach of Clause 8.1 as they were disparaging to generic companies in general and to Baker Norton specifically, as Norton was a major researcher in the asthma field, having developed equivalent products for all key asthma molecules. Baker Norton provided support and material for use with patients by doctors, eg adult and paediatric peak flow mouthpieces, respiratory tract posters, asthma clinic educational master cards, peak flow calculators and placebo inhalers. Consequently, the claim by Allen & Hanburys was misleading and disparaging and was in danger of bringing the pharmaceutical industry into disrepute.

Baker Norton further alleged that the advertising and promotional campaign was in breach of Clause 2, and was in serious danger of not only bringing discredit upon the pharmaceutical industry and profession but also reducing confidence in the ability and actions of the licensing authority to protect the interests of public health by approving medicine on the basis of safety, efficacy and quality.

Allen & Hanburys submitted that the statement was clearly not directed at any one company in particular. It was a plain statement of fact with regard to the ancillary services and support which Allen & Hanburys provided to the asthma community, both patients and healthcare professionals. It did not disagree that Baker Norton might provide mouthpieces, posters and cards, calculators and placebo devices; this did not attain the level of support which Allen & Hanburys provided, but even if it did, the statement clearly said that "...generic products do not usually offer the support, materials and services to healthcare professionals". Pharmaceutical companies were in the business of selling medicines, and it could not be disparaging to say that they did not usually provide healthcare support services in addition. Rather than being disparaging, the company was positively stressing the benefits of the support services which were provided by Allen & Hanburys.

The Panel had noted that the statement said "....generic products do not usually offer the support materials and services to healthcare professionals". The Panel had not considered that the statement was an attempt to disparage the generic medicines industry, although it could have been phrased more felicitously. It had accepted that Baker Norton did make material available but had considered that the statement, including the use of the word "usually", was on balance fair. The Panel had therefore ruled no breach of Clause 8.1 of the Code.

The Panel had not accepted that Allen & Hanburys' campaign was in breach of Clause 2 and therefore ruled no breach of that Clause.

*Appeal* Baker Norton said that the ABPI had many generic manufacturers who were members and the great majority were owned by major multinationals. The ABPI had the same obligation in representing those companies as it did its other members. It was therefore surprising that the Panel did not consider that the remarks were disparaging, although Baker Norton noted the comment that it was felt that the statement could have been phrased more felicitously. Perhaps the comment would have been fair if it had not been in the context of asthma inhalers. In this instance there were very few manufacturers for the different molecules that Allen & Hanburys marketed. For example, the only manufacturers of beclomethasone inhalers were Allen & Hanburys, Baker Norton and 3M Health Care. None of these companies could be regarded as not offering support to the medical profession, or carrying out significant research and developments of their own.

Allen & Hanburys said that the comment regarding the support materials and the services which it offered to health care professionals was a plain statement of fact which was intended as a positive statement on its behalf and certainly not intended to disparage generic companies. Baker Norton's final statement that its comment would have been fair if not in the context of asthma inhalers it found incomprehensible. Even if there were only two manufacturers involved in the production of generic MDIs, the fact remained there were at least eleven different marketing companies who were in the business of selling generic MDIs, none of whom were, to Allen & Hanburys' knowledge, providing anything like the ancillary support and services which Allen & Hanburys did. Hence its statement (in particularly the use of the word "usually") was more than fair.

*Appeal Board Ruling* The Appeal Board accepted that Baker Norton did make materials available but considered that the statement, noting its use of the word "usually", was, on balance, fair. The Appeal Board considered that the statement was acceptable and there had thus been no breach of the Code. The appeal therefore failed.

**Complaint received** **24 February 1994**

**Case completed** **23 June 1994**

**CASE AUTH/136/3/94**

**B BRAUN V NON-MEMBER COMPANY**

**Journal advertisement**

*Complaint* B Braun Medical Ltd, a non-member company, submitted a complaint concerning an advertisement issued by a non-member company. B Braun alleged that the advertisement was in breach of Clause 5.3 of the Code as it was an abbreviated advertisement with an area of 1247.7 square centimetres which was larger than the required size of 420 square centimetres.

*Response* The company submitted that the advertisement clearly promoted a container and invited respondents to suggest products they would like to see in this form. Every stab point appearing round the illustration of the container referred purely to the container.

*Ruling* The Panel considered the advertisement was for the container and was not an advertisement for a medicine. The Panel therefore ruled no breach of the Code.

**Complaint received** **29 March 1994**

**Case completed** **24 May 1994**

CASE AUTH/138/3/94

SMITHKLINE BEECHAM V THE WELLCOME FOUNDATION LIMITED

**Patient Experience Survey ruled to be disguised promotion**

*Complaint* SmithKline Beecham Pharmaceuticals complained about a general practice survey on Zovirax conducted by The Wellcome Foundation Limited.

The survey protocol described it as a "Patient Experience Survey to assess the acceptability of the new formulation of Zovirax 800 mg tablets and the treatment of Herpes Zoster in general practice and the clinical experience of the disease in a treated population".

SmithKline Beecham alleged that the survey was disguised promotion with its primary objective being to encourage prescribing of aciclovir in preference to other antiviral therapy and that the payments made for participation in the survey were an inducement to prescribe Zovirax. The basis of SmithKline Beecham's concerns was as follows:-

- the study appeared to lack any sound scientific basis; it was unclear whether it was a SAMM (Safety Assessment of Marketed Medicines) study, a Phase IV study or an observational one. There was no hypothesis and no planned statistical analysis and there was no rationale for the inclusion of 10,000 patients in a study of acceptability of a formulation change to a product with a generally accepted excellent safety profile. 10,000 represented 10% of the annual number of shingles patients and a higher proportion of those presenting early.

- that the payments for participation in this study were being presented by Wellcome representatives as an inducement;

- the approach to doctors with materials for the study was being made by Wellcome representatives and the company was aware of at least one instance where an approach was made unsolicited.

*Response* The Wellcome Foundation Limited submitted detailed information in support of its study including reasons as to the choice of the particular type of study. An observational study was chosen as the most suitable given the circumstances. There were two primary reasons for conducting the study. One was that the formulation had recently changed and the product could now be dispersed in water as well as being taken whole and secondly, it was considered an excellent opportunity to collect data, particularly on long term pain. The company emphasized that the protocol clearly stipulated to participating general practitioners that patients must only be entered into the study once they had already decided to prescribe Zovirax. Only those doctors who were known prescribers had been mailed about the study. The company submitted that SmithKline Beecham's assertion that 10,000 represented 10% of all shingles patients was exaggerated.

With regard to the allegations concerning the involvement of Wellcome representatives, the company supplied a detailed explanation as to the role of its representatives. Representatives only acted as postmen delivering study boxes to GPs who had indicated to head office that they wished to participate in the study. The company did have documented evidence of some GPs who, upon delivery of documentation, could not recall agreeing to participate in the study. These situations were investigated and a letter would be sent to the relevant GP together with a copy of the original signed and ticked reply card indicating their interest in participating in the study.

The company submitted that in most instances it had received apologetic notes from the doctors who could not recall completing the reply paid card.

The company pointed out that the fees paid to doctors under the study of £21.50 were in line with the BMA fee guidelines and constituted payment for the completion of an initial form at first visit and the collection and return of two other forms completed by the patient.

*Panel's Ruling* The Code of Practice Panel made a number of observations. Firstly, there did not appear to be sufficient scientific justification as to why a new but not novel presentation of a well established product justified a survey of 10,000 patients which represented a significant percentage of all shingles patients presenting early. Secondly, if the secondary purpose of the survey was to obtain further information on the product's effect on post-herpetic neuralgia (PHN) as submitted by the company, it was not clear as to the value of this data. In the company's submission it stated that it had already recently supplied the Medicines Control Agency (MCA) with the relevant evidence to support claims on the evidence for a reduction of the severity and incidence of PHN. The Panel observed that any data obtained from this survey would be of limited value in this regard as it was not in any way a controlled clinical trial.

Thirdly, the Panel noted that the survey was directed at the population of doctors known to be prescribers of systemic antiviral treatment for shingles and that the survey coincided with the launch of the first major competitor to Zovirax in the treatment of shingles. Although the protocol emphasised that doctors must only enter patients once they had already decided to prescribe Zovirax, it was inescapable that participation in the study would have some influence on the doctors' prescribing decisions.

The Panel considered that on balance the study was primarily a promotional exercise designed to promote and protect the market for Zovirax. The Panel therefore ruled there was a breach of Clause 10.2 which prohibits the use of studies as disguised promotion. It thus followed that the payment of doctors for participation in the study was inappropriate. A breach of Clause 18.1 was therefore ruled.

With regard to the allegations concerning the role of the representatives, the Panel did not accept that there was any evidence to show that they were acting inappropriately.

*Appeal* Wellcome submitted that there was a proper scientific/clinical justification for the study and that it was not a promotional exercise designed to promote Zovirax. The rationale behind the study was to find out information on acute disease outcome on the treated population, descriptive parameters of the disease in the community and descriptive outcomes in a treated population and to find out about patient acceptability of the new dispersible formulation.

The study was first conceived in May 1993 long before any discussions on the PHN issue with the MCA and some eight months before the launch of Famvir. Prior to the launch of Famvir there was only one established oral antiviral therapy available to participating GPs and even after the launch of Famvir participating GPs in the study were free to choose the antiviral therapy they felt was most appropriate for a particular patient.

The observational study was never intended to produce data to support claims on PHN. It was, however, seen as an opportunity to gather information on the long term pain outcome relevant to the acute management of the disease in a treated population. From discussion with practising physicians and clinical trial designers within the company, it was deemed unethical to set up a placebo controlled trial in a group of patients who would benefit from treatment in a severe acute stage of the disease. It would also have been inappropriate to have a comparison between the old and new formulation as that would have been an interventionist study. The chosen form of the study looked at the realities of the management of an acute disease (shingles) and the effect that management had on a long term outcome. In addition, there was the possibility of comparing a group of patients who received therapy in the prodrome and their long term outcome with a wide range of other distinct groups who received treatment at varying stages of the acute disease. The launch of a dispersible form of Zovirax 800mg tablets had provided an ideal opportunity to look at both patient outcomes on the treatment of disease and whether the new formulation offered any advantages to the patient. Detailed information was submitted on the number of patients recruited in the study. 14,500 GPs were mailed out of a total UK population of some 33,000 GPs. Although the target number of patients was 10,000, this represented the upper limit. The target figure of 10,000 in itself represented only 4.1% of the annual shingles market or 8% of currently treated patients.

The company pointed out that the cost of running the study had been far from meagre. If it had been the company's strategy to protect its shingles market, it could have adopted alternative measures which would have utilised the manpower and financial resources much more effectively.

The interim report on the observations made so far under the study was submitted.

*Appeal Board Ruling* The Appeal Board considered the submissions put forward by the company and in particular those relating to the rationale behind the survey and the various documents relating to it. The Appeal Board considered that although various reasons were put forward by the company on appeal concerning the purpose of the study, the primary objective as stated in the study protocol and in the letter sent to doctors requesting their participation in the survey was that it was designed to assess the acceptability of the new dispersible formulation. The gathering of information on the clinical experience of the treated population was secondary. Further, the Appeal Board considered that the actual questions to patients under the study about the dispersible tablet were very limited in scope.

With regard to patient numbers, the protocol did state that the aim was to recruit 10,000 patients over the twelve month study which was a high figure.

The Appeal Board considered that the survey was primarily a promotional exercise for Zovirax and upheld the Panel's ruling that it constituted disguised promotion in breach of Clause 10.2 of the Code. Although the actual level of payments to doctors for participation in the study was not unacceptable, it followed that as the study was disguised promotion, the offer of such payments was in breach of Clause 18.1. The Appeal Board therefore upheld the Panel's ruling. The appeal therefore failed.

**Complaint received** **30 March 1994**

**Case completed** **25 August 1994.**

CASE AUTH/140/3/94

THE WELLCOME FOUNDATION LIMITED V SMITHKLINE BEECHAM PHARMACEUTICALS

Various claims for Famvir

The Wellcome Foundation Limited complained about a number of claims for Famvir made by SmithKline Beecham Pharmaceuticals in various promotional items. Breaches of Clauses 2, 3.2, 4.2, 7.2, 7.3, 7.6, 7.7, 7.8, 8.1 and 15 were alleged. The promotional items were a detail aid (Ref 1093 FM:DA/3/014, a product monograph (Ref FM:MN/3/029), a journal advertisement (Ref 0194FM: AD/4/061 and 0194 FM:AD/4/058) and a GP giveaway of a box of gloves.

DETAIL AID

A) "Bioavailability is not reduced when taken with food"
"Superior bioavailability to acyclovir"

i) The Panel did not accept an allegation that the claim "Bioavailability is not reduced when taken with food" was misleading and not substantiated by current evidence. It was a statement of fact that the two studies by Fowles *et al* (on which the paper by Pue *et al* referenced to the claim in the detail aid was based) showed that bioavailability of famciclovir was not reduced when taken with food. No breach was ruled.

ii) With regard to an allegation questioning whether there were significant clinical advantages to be gained regarding Famvir's penetration to infection site based on bioavailability data, the Panel noted that the Appeal Board had not accepted that the claim "Excellent penetration to infection site" was substantiable by *in vitro* data alone in case AUTH/105/1/94 (see also Detail Aid point C) ii) below for further details). This ruling appeared to equally apply in this instance. The Panel therefore reaffirmed there was a breach of Clause 7.2 of the Code as previously ruled by the Appeal Board.

iii) The Panel did not accept an allegation that the inference that Famvir was superior to aciclovir was misleading as aciclovir was at least 100 times more potent. The Panel considered the actual claim in the detail aid "Superior bioavailability to acyclovir" was factually correct and in the context of the item was not misleading. No breach was ruled.

B) "Higher plasma concentrations than acyclovir"

i) The Panel had difficulty in following the allegation. Wellcome alleged that the graph showing plasma concentrations in conjunction with a graphic on the facing page in the detail aid was misleading as it was alleged that it could be interpreted as meaning that the penetration of famciclovir to the infected dermatome was excellent whereas the *in vitro* data referenced showed only the accumulation of penciclovir triphosphate in infected cells after the addition of penciclovir to tissue

culture medium. No breach had been demonstrated and thus the Panel ruled no breach.

ii) The Panel did not accept an allegation that the above graph was wrong. The graph refered to and was labelled as referring to single dose studies. No breach was ruled.

iii) SmithKline Beecham accepted that there was an error in the information given under the graph on plasma concentration which stated "Two separate groups of subjects were studied: n=18 for acyclovir, n=20 for famciclovir" as the figure for acyclovir was in fact 36. The Panel considered that although there was an error it was minor and conferred no advantage to the advertised product. The Panel did not therefore consider that it was misleading and ruled no breach.

iv) The Panel also did not accept the allegation that the graph showing mean plasma concentrations of aciclovir and penciclovir (the converted famciclovir) following single oral administration was in breach of Clauses 7.2 and 7.6 because it did not represent the true clinical situation. In this regard, the Panel noted SmithKline Beecham's submission that the view put forward by Wellcome that accumulation of aciclovir during the usually recommended course of seven days treatment resulted in higher peak concentrations for most of the time compared with penciclovir, remained unproven as no direct comparison of steady state plasma concentrations of the two medicines had been performed. The Panel also noted that the graph was clearly labelled as referring to single dose studies. No breach was ruled.

C) i) <u>"A more powerful anti-viral effect than acyclovir"</u>

ii) <u>"A powerful new alternative in the management of shingles"</u>

The Panel noted the Appeal Board's ruling in relation to Case AUTH/105/1/94 concerning the use of various claims for Famvir based on *in vitro* data. This included the detail aid currently under consideration in this case.

The Appeal Board had acknowledged that it was not possible to demonstrate the inhibition of varicella zoster viral DNA replication or prolonged antiviral effect other than by *in vitro* studies generally. The Appeal Board had also accepted that the data might be of relevance to the clinical situation. The Appeal Board did not accept, however, that it would be self evident to those to whom the promotional material was directed that such claims as "Excellent penetration to infection site" and "More powerful and prolonged antiviral effect" were based on *in vitro* data. Although it was indicated in the promotional material that the latter claims were based on *in vitro* data, by way of small footnotes, this was inadequate. It was a well established principle under the Code of Practice that one could not correct a misleading or inadequate statement by qualifying it in the small print. Furthermore, the Appeal Board did not accept that the claim "Excellent penetration to infection site" was substantiable by *in vitro* data alone. The Appeal Board had therefore upheld the Panel's earlier ruling in the case that there was a breach of Clause 7.2 of the Code.

The Panel considered that the claim "A more prolonged antiviral effect than acyclovir" as referred to by the complainant on one page in the detail aid, was sufficiently qualified by the information beneath it showing that it was based on *in vitro* data. The Appeal Board's ruling above applied elsewhere in the detail aid.

With regard to the use of one pulse per day of penciclovir (3mcg/ml) in the *in vitro* studies quoted, the Panel noted, as pointed out by the complainant, that the Famvir product monograph referred to 3mcg/ml as equivalent to a 500mg dosage (not the 250mg licensed dosage for Famvir). The Panel considered that the data presented in the detail aid was factually correct and, as noted above, that it was clear that it was derived from *in vitro* studies. There was no evidence to show that it was misleading. The Panel therefore decided that no case had been made by the complainant and ruled no breach.

The Panel did not accept there was any breach as alleged with regard to the claim "A powerful new alternative in the management of shingles" on the detail aid cover. No breach was ruled.

D) "A potent inhibitor of viral DNA replication"

i) The Panel noted that Wellcome alleged that as aciclovir triphosphate was at least 100 times more potent than penciclovir triphosphate against the target enzyme viral DNA polymerase, this was "likely to more than compensate for the five to six-fold longer intracellular half-life of penciclovir triphosphate". The response from SmithKline Beecham was that penciclovir was phosphorylated to a much greater extent that aciclovir and that this fact together with the superior bioavailability of penciclovir and the longer intracellular half-life of its triphosphate more than counterbalanced the greater potency shown by aciclovir triphosphate towards DNA polymerase *in vitro*.

The Panel considered that an allegation based on the conjection of what was "likely to" occur required further evidence. The statements in the detail aid were statements of fact relating to the *in vitro* data and, on the page cited by the complainant were clearly referred to as *in vitro* data. The Panel considered that no case had been made out that there was a breach of Clause 7.2 as alleged. No breach was ruled.

E) "Faster pain relief with a lower and less frequent dose than acyclovir"

i) The Panel noted that Wellcome had previously submitted a detailed complaint concerned with various comparative claims for pain relief with Famvir which had recently been considered by the Panel (Case AUTH/142/4/94). In that case, the Panel had reaffirmed decisions taken by the Appeal Board in an earlier case concerning Famvir (Case AUTH/105/1/94) in which a breach of Clause 7.2 of the Code was upheld by the Appeal Board in relation to various comparative claims for pain relief with Famvir. The complainant in Case AUTH/105/1/94, had also made an allegation that the claim for relief of pain were claims for an analgesic effect with Famvir. This had been rejected by the Panel and had not been appealed by the complainant. In the case currently under consideration, Wellcome now raised the additional allegation that the claims for comparative relief of pain was a claim for analgesic effect for which Famvir was not licensed in breach of Clause 3.2.

The Panel reaffirmed there was no breach of the Code with regard to the latter allegation as determined in Case AUTH/105/1/94 and reaffirmed the rulings relating to comparative claims for pain relief in Cases AUTH/105/1/94 and AUTH/142/2/94 that there was a breach of Clause 7.2.

The Panel did not accept that the allegation that the use of photographs showing the resolution of a shingles rash alongside the claim concerning pain relief implied that the reduction and resolution of the pain was directly related to the disappearance of the rash. No breach was ruled.

F) i) Daily dose frequency table

The Panel noted that it had ruled no breach in relation to allegations concerning claims for daily dosage frequency in Case AUTH/105/1/94 (This had been accepted by the complainant who had appealed other aspects of the Panel's rulings). The Panel therefore reaffirmed there was no breach in relation to this aspect of the claim.

ii) "Requires less drug, less often, for effective results"

The Panel noted the supplementary information to Clause 7.2 which states that "Claims for superior potency in relation to weight are generally meaningless and best avoided unless they can be linked with some practical advantage..." The Panel considered that in the absence of evidence demonstrating any clinical advantage, the claim for Famvir as requiring "less drug" was misleading in that it implied some clinical advantage and ruled there was a breach of Clause 7.2 as alleged.

**PRODUCT MONOGRAPH (REF FM:MN/3/029)**

A) "There is a clear need for effective, potent and easily administered treatment for herpes virus diseases"

The Panel did not accept the allegation that the above statement implied that there were no therapies to fit this description or that it suggested that famciclovir was licensed for other herpes viruses outside the terms of its licence in breach of Clauses 8.1 and 3.2. The statement appeared in the introduction to the monograph and in that context was clearly discussing the role of herpes virus infections generally and their need for treatment. No breach was ruled.

B) Figure 16 on adverse events

The Panel noted that claims regarding the safety profile of Famvir compared with aciclovir had been the subject of complaint in Cases AUTH/105/1/94 which had gone to appeal. The Appeal Board had considered that famciclovir had been shown in clinical trials to be well tolerated as claimed in the promotional literature and had therefore upheld the Panel's ruling of no breach in that case.

The Panel considered that the rulings in the above cases applied to the allegations now made

by Wellcome that it was misleading to imply that Famvir was comparable to Zovirax with regard to safety as implied in a table in the monograph showing a comparison of adverse events reported by Famvir and aciclovir in clinical trials.

JOURNAL ADVERTISEMENT (REF 0194 FM:AD/4/061 & 0194 FM:AD/4/058)

A) "Famvir is the first alternative to acyclovir"

The Panel accepted the allegation that the above claim was erroneous in that an alternative antiviral to aciclovir had been available for many years in the form of idoxuridine, albeit that its efficacy was queried. The Panel therefore ruled that it was inaccurate in breach of Clause 7.2.

B) "Compared with acyclovir, Famvir results in superior bioavailability (77% versus 15-30%) and achieves higher and more rapid plasma concentrations"

The Panel considered that the rulings made under points A) and B) of the detail aid applied to the allegations that the above claims were misleading by implication although factually correct.

GP PROMOTIONAL GIVEAWAY - BOX OF DISPOSABLE GLOVES (REF 1293 FM:GB/3/036)

A) "Compared with acyclovir More powerful and prolonged antiviral effect"
B) "Requires less drug, less often for effective results"
C) "A more prolonged antiviral effect than acyclovir"

Points A) and B) above as referred to in the complaint were considered under the detail aid point C i) ii) and F.

With regard to the allegations that the claim "A more prolonged antiviral effect than acyclovir" was misleading, the Panel considered that the Appeal Board's ruling in Case AUTH/105/1/94 as outlined under point C i) of the detail aid above applied.

PRESCRIBING INFORMATION

The Panel rejected the allegation that the prescribing information for Famvir failed to include certain adverse reactions. The data sheet for the product clearly stated that "headache and nausea had been reported in clinical trials. These were generally mild or moderate in nature and occurred in a similar incidence in patients receiving placebo treatment". No breach was ruled.

REPRESENTATIVES' ACTIVITIES

The Panel did not accept the allegations, unsupported by any evidence, that SmithKline Beecham representatives were promoting Famvir for post herpetic neuralgia and that they were still promoting the product as being cheaper than Zovirax despite a price reduction in Zovirax. In relation to the latter, the Panel noted the copies of memos to its field force submitted by SmithKline Beecham requiring immediate action in relation to the price change for Zovirax. No breach was ruled.

**Complaint received** **30 March 1994**

**Case completed** **8 June 1994**

CASE AUTH/142/4/94

THE WELLCOME FOUNDATION LIMITED V SMITHKLINE BEECHAM PHARMACEUTICALS

Comparative claims for pain relief with Famvir

*Complaint* The Wellcome Foundation Limited submitted a complaint in respect of comparative claims for pain relief with Famvir appearing in various promotional items. These were:-

- Detail aid

  "Faster pain relief with a lower and less frequent dose than acyclovir"
  "Faster relief of herpetic pain"
  "Faster relief of herpetic pain with early treatment"

- GP/Pharmacy mailing

  "EFFECTIVE: fast relief of herpetic pain"
  "Faster relief of herpetic pain with early treatment"

- Surgery poster

  "Faster relief of herpetic pain with treatment started within 48 hours"

- GP laminated leave-piece

  "Faster relief of herpetic pain with treatment started within 48 hours"

- Press release to consumer media (Dated 13/1/94)

  News release:

  "In a controlled trial of people treated within 48 hours of onset of rash there is evidence of a significantly more rapid relief of zoster associated pain than with acyclovir".

  Medical correspondent's monograph:

"...in patients treated within 48 hours of onset of rash, there is evidence of significantly more rapid relief of zoster associated pain than with acyclovir".
"In patients who started therapy within 48 hours of rash onset famciclovir was significantly superior to acyclovir in time to loss of pain"
"The product provides significantly faster relief of zoster associated pain than acyclovir in patients starting treatment within 48 hours of rash onset".

Wellcome alleged that the claims were exaggerated and had not been substantiated in breach of Clauses 7.2 and 7.3 as they were based on data derived from a subgroup analysis in a comparative trial by Nye *et al.* Various criticisms were made regarding this data. A breach of Clause 7.4 was also alleged as data requested from SmithKline Beecham had not been supplied. A breach of Clause 2 was also alleged.

*Response* SmithKline Beecham responded in detail to the allegations. With regard to the request for data from Wellcome, the company submitted that if some information had not been provided it was because the requests were either ambiguous or not accompanied by sufficient justification. Whilst the company was happy to provide Wellcome with data sufficient to substantiate its claims it was reluctant to comply with requests for data which were not directly relevant.

*Panel Ruling* The Code of Practice Panel noted that allegations regarding claims for pain relief had been considered in relation to various promotional materials for Famvir in Case AUTH/105/1/94. With the exception of the GP laminated leave-piece, all of the items referred to in the Wellcome complaint had been before the Panel and the Appeal Board in Case AUTH/105/1/94.

At the appeal for Case AUTH/105/1/94, the Code of Practice Appeal Board had accepted that the sub group analysis of the Nye study showed that famciclovir had a faster relief of herpetic pain with early treatment compared with the aciclovir group. The Appeal Board considered, however, that it was not sufficiently clear in the promotional literature that the faster relief of herpetic pain referred to a reduction in pain on a continuum and not immediate relief. Furthermore, the material did not in all places refer to the need for early treatment as being within 48 hours of onset. The Appeal Board considered that the data was insufficient to substantiate the unqualified claims for pain reduction in the promotional material and therefore upheld the ruling that there was a breach of Clause 7.2 of the Code.

The Code of Practice Panel considered that the Appeal Board ruling outlined above applied to the allegations made by Wellcome in this case. The Panel therefore reaffirmed that there were breaches of Clause 7.2 of the Code in relation to the comparative claims for pain relief with Famvir for the reasons outlined above. The Panel did not accept that there was a breach of Clauses 7.4 or 2 as also alleged.

**Complaint received** **6 April 1994**

**Case completed** **27 May 1994**

CASE AUTH/144/4/94

THE WELLCOME FOUNDATION LIMITED v MEMBER COMPANY

Booklet distributed at international congress

*Complaint* The Wellcome Foundation Limited complained that a booklet distributed by a member company at an international congress was in breach of Clauses 3.2, 7.2 and 7.3 of the Code as it implied a much wider indication range for the competitor product than for which it was licensed and as various claims were unsubstantiated.

*Response* The respondent explained that the booklet consisted of extracts of scientific papers presented at a symposium held in association with an international congress held outside the UK. The symposium was open to congress delegates and the booklet was given to those individuals attending the symposium. It had not been distributed in the UK.

*Panel Ruling* The Panel noted that the booklet had only been distributed to individuals attending an international meeting held outside the UK and had not been otherwise distributed in the UK. The supplementary information to Clause 1.1 on the scope of the Code specified that promotional material distributed at international meetings outside the UK did not come within the scope of the Code. The booklet in question was not, therefore, subject to the Code.

The Panel accordingly ruled that it did not come within the scope of the Code.

**Complaint Received 12 April 1994**

**Case completed 23 May 1994.**

CASE AUTH/145/4/94

DIRECTOR OF PHARMACY SERVICES V MEMBER COMPANY

Journal advertisement

*Complaint* A director of pharmacy services at a hospital submitted a complaint about an advertisement issued by a member company for one of its prescription only medicines which had appeared in a publication for healthcare workers.

The complainant alleged that the advertisement was in breach of the Code as the journal was on general sale from newsagents to members of the public whether or not they happened to be employed as healthcare workers. Further, the complainant alleged that the advertisement might encourage members of the public to ask their doctors for the product. The complainant enclosed statistics on the breakdown of readership of the publication.

The complainant alleged breaches of Clauses 22.1 and 22.2 of the First Revision of the Seventh Edition of the Code. The relevant clauses of the 1994 Edition were Clauses 20.1 and 20.2 respectively.

*Response* The company concerned submitted that as shown by the statistics on the breakdown of the readership of the journal, the readership clearly fell within the definition of health professional as set out in Clause 1.4 of the Code.

The company submitted that it was the likely readership which was the relevant test which should be considered and not the fact that the publication was available to the general public per se as

otherwise companies which placed advertisements in journals such as the British Medical Journal and The Lancet would fall foul of this restriction as those journals could also be bought by the general public.

With regard to the wording of the advertisement, the company submitted that it was justifiable and was in no way intended, nor could it reasonably be construed, as encouraging the general public to request that a doctor prescribe the product.

*Ruling* The Panel noted that the publication was a specialist professional title and was not aimed at the general public. The Panel considered that the important factor was to whom the publication was aimed and not whether or not the publication could be purchased by the general public. In this regard, the Panel noted that the British Medical Journal could be purchased by the general public but it was primarily intended for the medical profession.

The Panel did not accept that the advertisement was an advertisement to the public as alleged and considered that the publication was an acceptable vehicle for advertisements of prescription only medicines. The Panel therefore ruled no breach of the Code.

**Complaint received** **14 April 1994**

**Case completed** **27 May 1994**

CASE AUTH/146/4/94

THE WELLCOME FOUNDATION V SMITHKLINE BEECHAM PHARMACEUTICALS

**Product monograph and another document on Famvir**

The Wellcome Foundation Limited complained about two documents on Famvir issued by SmithKline Beecham Pharmaceuticals. One was a product monograph and the other a typescript of what was described by the complainant as an abridged monograph. Aspects of the full product monograph had been previously complained about by Wellcome in Case AUTH/140/3/94.

**Product Monograph**

*Complaint* Wellcome alleged that references in the product monograph to the activities of famciclovir (Famvir) against herpes simplex virus (HSV) were in breach of Clause 3.2 of the Code as Famvir was only licensed for the treatment of shingles. Further, that data presented in the monograph comparing the effects of penciclovir (the converted famciclovir) with aciclovir in various viruses were disparaging of aciclovir in breach of Clause 8.1 as although the results demonstrated activity in favour of penciclovir, aciclovir was in fact proven clinically effective against certain viruses for which Famvir was not licensed.

Attention was also drawn to the statement "In common with acyclovir and ganciclovir, penciclovir is not well absorbed (only about 5%) after oral administration" which Wellcome alleged gave the impression that aciclovir had a bioavailability of only 5% whereas it was in fact around 20%.

*Response* SmithKline Beecham submitted that the monograph was intended as a factual booklet to provide doctors with the scientific and clinical background to Famvir and that it quite

clearly stated that Famvir was licensed for the treatment of herpes zoster. Nowhere was there any claim made for its use in other viral infections nor was any clinical trial data given for any indication other than herpes zoster infections. In this context it was reasonable to provide a representative overview of the preclinical investigations of penciclovir through which its pharmacological properties were determined. Some of the pharmacological properties of penciclovir could only be demonstrated in cells infected with other herpes viruses such as herpes simplex virus because it was not possible to perform detailed studies in varicella zoster virus because of its highly cell associated nature. To omit references to these studies would be to fail to give a complete evaluation of all scientific evidence on the development of the product and this would have diminished the value of the monograph.

The company submitted that the statement regarding the absorption of penciclovir was a statement of fact.

*Ruling* The Panel had some concern at the amount of information relating to HSV in a product monograph for a medicine licensed only for herpes zoster and as it appeared many of the references to HSV seemed to be used to show advantages over aciclovir. The Panel also noted the statement which appeared in a separate box in the section on pre-clinical studies that "'Famvir' was developed to provide an effective, potent and convenient oral form for treating herpes virus infections" which came close to recommending it for a broader range of viruses than simply herpes zoster for which it was currently licensed. The Panel accepted, however, that it was not unreasonable to include in the monograph references to activity against HSV as part of establishing the product's overall antiviral activity and, as submitted by SmithKline Beecham, because it was not possible to perform detailed studies with varicella zoster virus due to the nature of that virus.

The Panel decided that on balance the monograph was not unacceptable and ruled that there was no breach. With regard to the statement "In common with acyclovir and ganciclovir, penciclovir is not well absorbed (only about 5%) after oral administration", the Panel considered that although it could have been better worded to avoid any possibility of it being read that the 5% referred to the other two products as well as penciclovir, the Panel decided that it was not misleading. No breach was ruled.

**Other document on Famvir (Ref: FAM1310.DOC)**

a) Prescribing Information

*Complaint* Wellcome alleged there was a breach of Clause 4.1 as the document picked up at a SmithKline Beecham Pharmaceuticals stand at a general practice meeting, failed to include prescribing information.

*Response* SmithKline Beecham explained that the document was produced as part of a reply following a request for information from a specific doctor and was not intended as a promotional item. It had been used at the general practice meeting in question without the company's knowledge or authorisation. Disciplinary proceedings were being taken to ensure that the mistake would not repeat itself. The representative had, however, attached prescribing information to the document when given out at the meeting.

*Ruling* The Panel noted that the document submitted by Wellcome did not include prescribing information although the copy submitted by SmithKline Beecham did include promotional claims and prescribing information on the reverse. The copy submitted by SmithKline Beecham differed also from the copy submitted by Wellcome in that the typographical error referred to under d) below had been corrected.

The Panel noted that the document submitted by Wellcome did not include prescribing information and ruled there was a breach of Clause 4.1 as alleged. The document had clearly been used for promotional purposes and prescribing information was thus required.

b) Pharmacokinetics

*Complaint* Wellcome alleged there was a breach of Clause 7.2 of the Code in that the section on pharmacokinetics in the document stated that the bioavailability of aciclovir was seriously affected by food unlike famciclovir although Wellcome's data suggested that after food 800 mg aciclovir gave higher plasma concentrations than 250 mg famciclovir on repeat dosing as in the clinical situation. The section also failed to mention the significant effect that food had on the plasma levels of penciclovir.

*Response* SmithKline Beecham pointed out that Wellcome's submission regarding repeat dosing was unproven as no direct comparisons of steady state plasma concentrations of the two medicines administered after food had been performed. Further, the abridged monograph clearly stated that the peak plasma concentrations of penciclovir were lower and were reached slighter later when Famvir was administered after food. Alterations in the absorption profile did not necessarily alter bioavailability.

*Ruling* The Panel noted that these allegations were previously raised by Wellcome in relation to a detail aid (Ref: 1093 FM:DA/3/014) in Case AUTH/140/3/94. The Panel's rulings of no breach in that case therefore applied.

c) Antiviral Activity

*Complaint* Wellcome alleged that the claim "At a clinically relevant concentration of 3µg/ml penciclovir was a potent inhibitor of VZV DNA synthesis, whereas acyclovir had minimal activity" in the document was in breach of Clauses 3.2, 7.2 and 7.8 of the Code as the use of such *in vitro* data was irrelevant to the clinical situation and an attempt to discredit aciclovir. Furthermore the data quoted was at a concentration which equated to a 500 mg dosage of famciclovir and not the 250 mg licensed dosage.

A breach of Clause 7.5 was also alleged with regard to a table which Wellcome alleged had been incorrectly referenced as all the information in the table was not found in the quoted reference.

*Ruling* The Panel noted that the allegation concerning the claim referring to penciclovir being a potent inhibitor of VZV DNA synthesis, had previously been raised by Wellcome in relation to the detail aid in Case AUTH/140/3/94. The Panel's rulings in that case therefore applied.

With regard to the alleged breach of Clause 7.5, the Panel noted the submission from SmithKline Beecham that the data and the table was derived from a number of sources, the majority of which were included in the paper cited in the document. Other data used in the table was obtained elsewhere.

The Panel considered that it was misleading to use the one reference as a reference to the data contained in the table as it implied all the data was obtained from that source. The Panel therefore ruled there was a breach of Clause 7.2.

d) Clinical Studies

*Complaint* Wellcome alleged that there were breaches of Clauses 7.2 and 7.6 in relation to the presentation of data in the document from the study by Nye et al on the significantly reduced times to loss of pain in those patients treated with Famvir within 48 hours of onset of rash. It was also pointed out that the abridged monograph stated that the time to complete loss of pain was 21 days, whereas in the product monograph it stated it was 12 days.

*Ruling* The Panel again noted that Wellcome had previously made a number of allegations concerning comparative claims for pain reduction in Cases AUTH/142/4/94 and AUTH/140/3/94 . The Panel's rulings in those cases therefore applied.

The Panel noted SmithKline Beecham's submission that the reference to 21 days to loss of pain instead of 12 days was a typographical error but nonetheless considered that the data as presented in the abridged monograph was inaccurate as to the actual results of that study and therefore ruled there was a breach of Clause 7.2.

**Complaint received** **15 April 1994**

**Case completed** **20 June 1994**

CASE AUTH/147/4/94

ZENECA PHARMA V VESTAR LTD

**Promotion of AmBisome**

Zeneca Pharma made a number of allegations about a promotional item for AmBisome issued by Vestar Ltd which compared AmBisome with amphotericin B colloidal dispersion (ABCD), a product to be launched by Zeneca in May 1994. The item was set out in two columns, one for each product, and compared certain features of the two products. Vestar UK, although not a member of ABPI, had nevertheless agreed to comply with the Code.

1. **Misleading layout**

*Complaint* Zeneca alleged that the layout of the item suggested that the two products AmBisome and ABCD had been directly compared and that conclusions might be drawn about them. There were no published studies which directly compared the two products and, contrary to the impression given, it was not known whether one agent was better tolerated or more effective than the other.

*Ruling* The Panel did not consider that the layout implied that a direct comparison had been made of the two products in these respects and did not accept that it implied that comparative tolerability data existed. The Panel therefore ruled no breach of Clause 7.2.

2. **Failure to provide an objective, balanced evaluation of all the scientific evidence**

*Complaint* Zeneca said that despite over thirty publications in the literature on ABCD, only two

references were quoted to support the statements made regarding ABCD. The item failed to provide a fair, balanced or objective assessment of all the data available on ABCD. Breaches of Clause 7.2 were alleged. For example, under the heading "Toxicity" a murine LD 50 value of 20 mg/kg was given for ABCD but separate published data indicated that the murine LD 50 was higher at 36-38 mg/kg. With regard to human exposure, under the heading "Tolerability" statements regarding ABCD were alleged to have been selectively chosen from a small study on healthy volunteers, ignoring further published data on patients, including those who had previously failed to tolerate conventional Amphotericin B, which indicated that ABCD was generally well tolerated. Under "Tolerability", the position of the statements ".....AmBisome has been shown to be very safe....." and ".....ABCD, however, showed (in a small clinical trial) a high incidence of adverse effects ....." referenced to a study by Janknegt implied that comparative tolerability data existed and was a misleading comparison. The conclusion in the Janknegt study stressed the lack of data on which to compare clinical efficacy and tolerability of various amphotericin formulations.

*Ruling* The Panel did not accept that it was necessary to cite all thirty publications on ABCD. However, Clause 7.2 of the Code required that information must be based on an up to date evaluation of all the evidence. Under Clause 7.5, references were only required when referring to published material.

In relation to the allegation regarding the murine LD 50, the Panel noted that Vestar accepted that the value might be higher than 20 mg/kg and stated that it would quote a value of 36-38 mg/kg in future. The Panel ruled that there had been a breach of Clause 7.2 as the murine LD 50 value given in the material was inaccurate.

In relation to the allegations concerning tolerability, Vestar referred to a paper by Herbrect which was data from an open prospective study conducted by LTI, the manufacturer of the drug. Bearing this new data in mind, Vestar considered that the promotional item was an objective, balanced evaluation.

The Panel considered that even if the statements regarding tolerability of the two products were both separately true, it was misleading to juxtapose them in the manner which had been adopted in the promotional item. The two products were being compared but on quite different criteria. It was misleading to compare different types of data in the manner which had been adopted. The Panel therefore ruled that there had been a misleading comparison in breach of Clause 7.2.

3. <u>Quotation not accurately reflecting the meaning of the author</u>

*Complaint* Zeneca said that some of the literature quoted in respect of ABCD had been selectively edited so that, as cited, it did not accurately reflect the meaning of the authors and was therefore misleading. Selective editing had in some parts of the item also changed the sense of the authors' conclusions. Breaches of Clause 11.2 were alleged.

Under the heading "In Vitro Efficacy", Zeneca drew attention to the quote ".... ABCD complexing variably affects AmB (Amphotericin B ) in vitro activity compared with that of ABDS. (amphotericin B desoxycholate suspension) ....." which implied uncertainly about the efficacy of ABCD. The study from which the quote was taken continued "Neither preparation was favoured in terms of numbers of isolates with higher or lower results in either the MIC or MFC assays.". Again under the heading "In Vitro Efficacy" in relation to ABCD, attention was drawn to the quote "..... markedly higher MFCs of ABCD were found in strains of <u>Candida albicans, Torulopsis glabrata</u> and <u>Coccidioides immitis</u>". Zeneca pointed out that the complete sentence in the study from which the quote was taken was "Although the mean MIC and minimal fungicidal concentrations (MFC) of both formulations are similar, markedly higher MFCs of ABCD were found in strains of <u>Candida Albicans, Torulopsis glabrata</u> and <u>Coccidioides immitis</u>". Zeneca alleged that omitting

the first part of the sentence implied generally poorer in vitro efficacy for ABCD thus distorting the authors' view.

*Response* Vestar said that the quotations under in vitro efficacy did reflect the true meanings of the authors. However, further comparisons could be made by reviewing newly published papers by Frances et al and Allende et al. From the data on colony forming units, it seemed that 1 mg/kg of conventional amphotericin B was equivalent to 5 mg/kg of ABCD. 1 mg/kg of ABCD was no different to control. In the light of this additional data, the company believed that the comparison made was still valid.

*Ruling* In relation to the statement under in vitro efficacy, the Panel considered that once again the statements made in relation to the two products were not on all fours. To use quotations edited to omit the qualifications which appeared in the actual study as a basis for comparing products was misleading. The Panel therefore ruled a breach of Clause 7.2 of the Code. A breach of Clause 11.2 was also ruled as the quotations did not reflect the meaning of the authors.

4. Distribution

*Complaint* In relation to "Distribution", Zeneca pointed out the promotional item stated "It is not known how ABCD can reach sufficient tissue concentrations ....." whereas the reference given actually stated "It is not fully clear how ABCD can reach sufficient tissue concentrations.....". The inaccurate substitution in this context of the words "not known" misled by implication to the conclusion that ABCD may be unable to reach sufficient tissue concentrations. There was further published literature to indicate that although tissue concentrations may differ from conventional Amphotericin B, ABCD was nevertheless effective against fungal pathogens in numerous tissues.

*Response* Vestar stated that the copy under the heading "Distribution" was not a quotation and it was therefore free to use the phrase "not known". The statement was referenced to Janknegt which stated that the AUC after a standardised dose of ABCD was 2-fold lower than ABLC (amphotericin B lipid complex) which in turn was 5-fold lower than AmBisome. It was not surprising that the author stated "It is not fully clear how ABLC and ABCD can reach sufficient tissue concentrations, especially in the acute phase of infection". Vestar knew that Zeneca revised the data on efficacy which LTI submitted to the Medicines Control Agency, lowering the estimate of response rate to fungal infection. Vestar submitted that there was enough uncertainty surrounding the efficacy of ABCD to be reassured that Janknegt was reasonable in his statement.

*Ruling* The Panel considered that the use of the words "not known" in the promotional material gave the impression that the efficacy of ABCD was in question. It did not accept that "not fully clear" was the same as "not known". The Panel considered that the statement "It is not known how ABCD can reach sufficient tissue concentrations ....." was misleading and did not accurately reflect the paper to which it was referenced. The Panel therefore ruled a breach of Clause 7.2 of the Code.

5. Use of the word "Safe"

*Complaint* Zeneca referred to the use under "Tolerability" of the claim that "AmBisome was very safe.....". This was a contravention of Clause of 7.7 of the Code.

*Response* Vestar said that the word "safe" was qualified. It was in the context

of a quotation which was referenced and there was a lot of data to support it. Therefore, the use of the word "safe" did not breach the Code.

*Ruling* The Panel noted that Clause 7.7 of the Code said that the word "safe" must not be used without qualification. To say "very safe" did not mean that the word "safe" had been qualified. It was in fact the opposite as it had been amplified. It was ruled that there had been a breach of Clause 7.7 of the Code.

6. Promotion inconsistent with data sheet particulars

*Complaint* Zeneca said that the cited claim "AmBisome has been known to be very safe in dosages up to 5mg/kg/day" represented a dosage recommendation which exceeded that in the AmBisome data sheet (up to 3 mg/kg day). The promotional item was therefore not consistent with the data sheet and in breach of Clause 3.2.

*Response* Vestar submitted that the item was consistent with the data sheet particulars which gave the usual dose as 1 - 3 mg/kg as required. Patients had received up to 15 mg/kg without adverse affects. The paper published by Mills et al showed doses up to 5 mg/kg could be given safely. The company had controlled studies at 5 mg/kg. It was up to Vestar to make dosage recommendations.

*Ruling* The Panel considered that the use of the dosage was acceptable given its inclusion in a statement relating to tolerability and the recommendation in the data sheet that "Dosage of amphotericin as Ambisome must be adjusted to the specific requirements of each patient". The Panel noted that the dosage recommendations were to some extent flexible. The Panel therefore ruled no breach of the Code.

**Complaint received** **18 April 1994**

**Case completed** **11 July 1994**

## CASE AUTH/148/4/94

## THE WELLCOME FOUNDATION LIMITED V SMITHKLINE BEECHAM PHARMACEUTICALS

### Launch press release pack for Famvir

The Wellcome Foundation Limited complained about two documents, a news release for the consumer media and a monograph for accredited medical correspondents, issued by SmithKline Beecham Pharmaceuticals as part of the launch press release pack for Famvir.

a) News Release - Consumer Media

*Complaint* Wellcome alleged that the claims "Famciclovir has a good safety profile like acyclovir", "a new generation of antiviral treatment for shingles" and "offers a significant advance" were in breach of Clause 7.2 of the Code. The claim about the famciclovir safety 1profile was also alleged to be in breach of Clause 20.2.

***Ruling*** The Panel noted that claims regarding the safety profile of Famvir compared with aciclovir had been the subject of complaint in Cases AUTH/105/1/94 and AUTH/140/3/94, and the rulings of no breach in those cases therefore applied.

The Panel considered that although it was not entirely clear what was meant by the phrase "a new generation", it did imply a major change or progression in antiviral treatment. The Panel considered that it was exaggerated to claim that Famvir was "a new generation of antiviral treatment for shingles" and ruled it was in breach of Clause 7.8. Similarly, the Panel did not accept that there was sufficient evidence to show that Famvir offered a "significant advance" and ruled there was a further breach of Clause 7.8.

b) Famciclovir - a Monograph for accredited Medical Correspondents

Mode of Action

***Complaint*** Wellcome alleged that the claim "..... (penciclovir triphosphate) (the converted famciclovir) prevents further DNA chain elongation and thus inhibits viral replication" was incorrect and in breach of Clause 7.2 as it implied that penciclovir was an obligate chain terminator. It was pointed out that there was the potential for penciclovir to be incorporated into the growing DNA chain.

***Response*** SmithKline Beecham submitted that the Oxford Dictionary definition of "prevent" included "stop, hinder" and there was no doubt that PCV-TP (penciclovir triphosphate) hindered DNA chain elongation as it would otherwise be ineffective in inhibiting viral DNA replication. Arguments about obligatory chain termination and the potential to be incorporated into the growing DNA chain were therefore redundant.

***Ruling*** The Panel noted the submission from SmithKline Beecham that the use of the term "prevent" meant "hinder" and that penciclovir hindered further DNA chain elongation and thus inhibited viral DNA replication. The Panel accepted that penciclovir inhibited viral DNA replication, but considered that the term "prevents" in the context in which it was used "...prevents further chain elongation...." meant that it stopped such elongation immediately. The Panel considered that the claim was therefore inaccurate and ruled it was in breach of Clause 7.2.

Cell Activity

***Complaint*** Wellcome alleged that the claims "Famciclovir is highly selective for infected cells" and "Penciclovir rapidly enters both infected and uninfected cells but is activated only in herpes virus-infected cells" were incorrect and in breach of Clause 7.2.

***Ruling*** The Panel considered that the claim "Famvir is highly selective for infected cells" was a statement of fact as submitted by SmithKline Beecham. The Panel therefore ruled there was no breach.

With regard to the claim "Penciclovir rapidly enters both infected and uninfected cells but is only activated in herpes virus-infected cells", the Panel noted the submission from SmithKline Beecham that it recognised that small amounts of penciclovir, as with other antivirals, could be phosphorylated to PCV-TP in cells uninfected with herpes virus. The Panel therefore considered that the claim was inaccurate and ruled there was a breach of Clause 7.2.

**Complaint received** **6 May 1994**

**Case completed** **20 June 1994**

CASE AUTH/149/4/94

SMITHKLINE BEECHAM PHARMACEUTICALS V THE WELLCOME FOUNDATION LIMITED

Claims ruled in breach

SmithKline Beecham Pharmaceuticals complained about the promotion of Zovirax by The Wellcome Foundation Limited. The promotional items concerned were a detail aid (ref M2601215C September 1993) a GP mailing consisting of a letter and a brochure and journal advertisements appearing in Pulse, 22 January 1994 and MIMS magazine weekly, March 1994.

1 "Zovirax - The subject of unprecedented safety monitoring"

*Panel's Consideration* SmithKline Beecham Pharmaceuticals alleged that the above claim appearing in both the detail aid and the GP mailing was in breach of Clauses 7.3 and 7.8 of the Code as whilst safety monitoring of Zovirax had been extensive, other medicines had also been extensively studied. Examples, such as cimetidine, were cited.

Wellcome acknowledged that other medicines had been the subject of extensive safety monitoring but that in the absence of equivalent published data for any other medicine the safety of oral aciclovir had been studied in more breadth (the number of studies) and depth (ability of studies to accurately identify and quantify serious events) than any other medicine. Copies of literature relating to the safety evaluation of Zovirax were submitted.

The Panel considered that the use of the term "unprecedented" meant that Wellcome was claiming that there had never been safety monitoring of the same order as that undertaken for Zovirax and that the safety monitoring was of the highest standard. Although the term "unprecedented" could mean that something was done exceptionally poorly, it was clear in the context of the claim that it meant the safety monitoring was of the highest standard.

The Panel noted the information submitted by Wellcome but considered that there was no way there could be certainty that another product had not had more complete safety monitoring given its particular circumstances. It was conceivable that a product used in the treatment of a very rare disease could have safety monitoring with information relating to every patient receiving it.

The Panel therefore decided that the claim "unprecedented safety monitoring" was unsubstantiated and ruled that there was a breach of Clause 7.3.

2 "Less than 0.01 % side-effects reported"

*Panel's Consideration* SmithKline Beecham alleged that the above claim appearing in both the detail aid and journal advertisements was exaggerated and in breach of Clause 7.8 of the Code as, if the frequency of side effects was as low as claimed, it would be highly unlikely that side effects would be detected in clinical trials and this was not the case. The aim appeared to be to minimise safety issues in breach of Clause 7.7.

Wellcome provided detailed information on the calculation of the figure which was based on the worldwide use of Zovirax and reporting rates for adverse events. It was simply stating a fact that reporting of adverse events had been rare with a reporting rate of less than 0.01%. It was not appropriate to calculate "incidence" rates from spontaneous safety reports. The company pointed out that the incidence of adverse events in all placebo controlled studies of aciclovir revealed a pattern of similarity between treated and placebo groups.

The Panel noted that the side effect reporting rate for any product would vary considerably according to the length of time it had been on the market. It was to be expected that the numbers of side effects reported would reduce considerably once a product's side effect profile was well established. The reporting rate did not therefore necessarily reflect the level of side-effects associated with the product.

The Panel considered that although the claim "Less than 0.01% side-effects reported" might be factually correct, the implication was that the incidence of side-effects was related to the 0.01% figure which as referred to above was not a fair assumption. The Panel considered that the disputed claim was therefore misleading by implication as to the side-effect profile of the product and ruled there was a breach of Clause 7.2 of the Code.

*Appeal By Respondent* Wellcome submitted that it was firmly recognised within the pharmaceutical industry that the major and legally required yardstick with which to measure the relative safety of products was to refer to the reporting rate of adverse events. Indeed this method was used by the Committee on Safety of Medicines to judge the safety profile of marketed products despite the known under reporting because there was no other proven method.

The events reported over the last four years for Zovirax had remained static at around the 0.01% figure and looking back one could see that the adverse event profile for Zovirax had remained remarkably consistent from launch to fifteen years on. The company submitted that if it was unable to use facts from the only available yardstick, then safety profiles could only be designed as good, equivocal or bad which would then put Zovirax in the same category as many other medicines. It had to be noted that Zovirax was in a therapeutic area which had been hounded by toxicity issues, where physicians have had to make choices about questionable benefits of an antiviral agent versus the prognosis of the viral infection if left untreated.

Further data in the form of a Prescription Event Monitoring Report issued by The Drug Safety Research Unit had confirmed the excellent safety profile associated with Zovirax.

*Appeal Board's Ruling* The Appeal Board accepted the Panel's conclusions that although the claim "Less than 0.01% side-effects reported" might be factually correct, the implication was that the incidence of side-effects was related to the 0.01% figure which was not a fair assumption. In this regard, the Appeal Board noted that the Prescription Event Monitoring study which was nearer to a real life situation than clinical trials showed side-effects reporting at a level well above 0.01%. Further, with regard to the accuracy of calculations, the Appeal Board noted that it was difficult to ascertain numbers of patient exposures world wide and it had to be acknowledged that side-effects reporting was heavily concentrated in the UK and North America.

The Appeal Board considered that the audience would interpret the use of the word "reported" in the claim as referring to data from clinical trials and not a reference to the reporting rates for adverse events.

The Appeal Board considered that the disputed claim was misleading by implication as to the side-effect profile of the product and upheld the Panel's ruling that there was a breach of Clause 7.2 of

the Code. The Appeal therefore failed.

(3) "Specificity, efficacy and safety combined give you the power over the virus"

*Panel's Consideration* SmithKline Beecham alleged there was a breach of Clause 7.7 in relation to the use of the word "safety" in the above claim in the detail aid. This was denied by Wellcome which submitted that the word "safety" was qualified by preceding information in the detail aid and by the information which would be presented by the representative during the course of the interview.

The Panel did not accept that any claim in written material could be qualified by what representatives said to doctors when promoting the product. Written claims had to stand by themselves.

The Panel considered that in the context of the claim "Specificity, efficacy and safety combined give you the power over the virus" the word "safety" meant "safe". Any qualification of the word "safe" or any grammatical derivative of that word such as "safety", needed to be in immediate conjunction with the use of the term. It was not sufficient to qualify the word in preceding text as submitted by Wellcome. The Panel therefore ruled there was a breach of Clause 7.7 as alleged.

(4) Prescribing Information

*Panel's Consideration* SmithKline Beecham alleged that the prescribing information in the detail aid failed to include the substance of the relevant information in the data sheet relating to side effects in breach of Clause 4.2 of the Code. Similar allegations were made in respect of the GP mailing and the journal advertisements.

Wellcome pointed out that the prescribing information given in the detail aid for Zovirax tablets and suspensions listed the major relevant side effects that might be expected in patients for whom those formulations were prescribed. These were rash and gastrointestinal side effects. The other side effects listed in the data sheet represented the accumulation of over fifteen years of spontaneous adverse drug event reporting with the majority of those side effects having occurred in patients with renal impairment or other predisposing factors or were rare or were not thought to be definitely attributable to Zovirax. These events had been reported mainly in patients on the intravenous formulation and were listed in the prescribing information for Zovirax IV which appeared on the back of the detail aid.

The Panel accepted that the summary of side effects given in the prescribing information for Zovirax tablets and suspension was appropriate as submitted by Wellcome and ruled there was no breach of the Code. The Panel similarly found no breach of the Code with regard to the prescribing information in the GP mailing and the journal advertisement.

(5) "It can only be Zovirax"

*Panel's Consideration* SmithKline Beecham pointed out that one series of journal advertising for Zovirax consisted of two advertisements separated by an intervening page of the journal. The above claim appeared on the second advertisement which SmithKline Beecham alleged was all embracing in breach of Clause 7.8. when it was read in isolation.

The Panel considered that the claim "It can only be Zovirax" was essentially an advertising slogan without specific meaning. The Panel did not consider that the claim was objectionable and ruled there was no breach.

**(6) "Which highly selective antiviral terminates viral DNA with just one molecule? It can only be Zovirax"**

*Panel's Consideration* SmithKline Beecham alleged that the above claim was all embracing and misleading as the term "viral DNA" implied that Zovirax could be used to treat DNA virus infections other than herpes zoster and herpes simplex for which it was licensed. Furthermore it implied that Zovirax would stop all viral replication in clinical use. It could also be taken to mean that a single molecule would achieve this.

Wellcome submitted that Zovirax was an obligate chain terminator unlike other anti herpes nucleoside analogues. The company also submitted that the prescribing information and the advertisement clearly showed that Zovirax was not licensed for the management of any other virus apart from herpes simplex types 1 & 2 and varicella zoster virus. This clarified the fact that the company was not implying that Zovirax could be used to treat other DNA viral infections.

The Panel accepted the submission put forward by Wellcome and ruled there was no breach of the Code.

*Appeal by Complainant* SmithKline Beecham appealed against the Panel ruling.

SmithKline Beecham argued that the claim that Zovirax "terminates viral DNA" clearly implied that in clinical use it stopped viral DNA replication and the Panel ruling did not deny this. The subsequent claim, "It can only be Zovirax" was therefore inaccurate as Famvir also stopped viral replication and, as with acyclovir triphosphate, one molecule of penciclovir triphosphate could stop replication of a viral DNA chain. That aciclovir triphosphate could be described as an obligate chain terminator was largely irrelevant. The fact was that both drugs acted by one molecule being incorporated into the growing viral DNA chain thus stopping completion of that chain. It was unlikely that many readers of the advertisement would interpret the phrase "terminates viral DNA" as having the narrow meaning of obligate chain terminator, even if they were familiar with the latter term.

SmithKline Beecham stated that it was most unlikely that only one molecule of aciclovir was involved in the termination of any individual viral DNA chain in production and that although a viral DNA chain which had been terminated might only contain one molecule of aciclovir, the same could be said for other nucleoside analogues including penciclovir. Further, the claim was based on *in vitro* data which in isolation had no clinical relevance.

Wellcome stated that it was not attempting to suggest in its material that a patient only required to be given one molecule of Zovirax in order to stop all viral replications. The statement was referring to the final outcome of the termination process which in the case of aciclovir took only one molecule as it was an obligate chain terminator. Although penciclovir might also terminate viral DNA with one molecule, this did not happen on every occasion. If this was to have clinical significance it would not be with regard to efficacy but to safety. Detailed information on the safety problems associated with other antivirals were submitted.

*Appeal Board Ruling* The Appeal Board accepted that the claim "Which highly selective antiviral terminates viral DNA with just one molecule? It can only be Zovirax" meant that it took only one molecule to terminate viral DNA replication. It did not mean that it took only one molecule in order to stop all viral replication. The Appeal Board did not consider that reference to the feature was inappropriate. The Appeal Board also accepted that although penciclovir would also terminate viral DNA with just one molecule, this did not necessarily happen on every occasion. The Appeal Board therefore considered that the claim that Zovirax terminated viral DNA with just one molecule was a statement of fact and upheld the Panel's ruling that there was no breach of the Code.

The appeal therefore failed.

**Complaint received** **20 April 1994**

**Case completed** **25 August 1994**

CASE AUTH/150/4/94

DIRECTOR V MEMBER COMPANY

**Article criticising the promotion of a product**

*Complaint* An article on a member company's product published in the Drug & Therapeutics Bulletin referred to the promotion of the product as being more potent than competitor products and less likely to cause systemic effects and stated that the claimed advantage was undermined by the lack of published comparisons.

In accordance with established procedure, the matter was taken up as a complaint under the Code.

*Response* The company submitted that the Code required that claims must be capable of substantiation. There was, however, no requirement for substantiating data to be published. The company submitted that all claims were clearly referenced to data either published or unpublished that could be used to substantiate the claims.

The company summarised the main studies used to support its promotional claims and pointed out that some of the data were to be published.

*Ruling* The Panel noted that it was well established that data used to substantiate claims in promotional material need not necessarily be published. It was possible for both published and unpublished data to be used.

The Panel noted that the allegations were of a very general nature. It appeared from the material supplied that the company had sufficient data to substantiate the claims. No breach of the Code was ruled.

**Complaint proceedings commenced** **29 April 1994**

**Case completed** **7 June 1994**

## CASES AUTH/151/5/94 AND 153/5/94

## CONSULTANT PAEDIATRICIAN & GENERAL PRACTITIONER V ALLEN & HANBURYS

### Promotion of products on a special front page of a daily newspaper

*Complaint* A consultant paediatrician complained about the promotion of Allen & Hanburys Limited's products by means of a special front page attached to a daily newspaper. The complainant alleged that this was a most unprofessional and unwelcome form of advertising which he hoped would not be repeated.

A general practitioner stated that he was alarmed to receive an unsolicited copy of a daily newspaper for the medical profession only. The newspaper was delivered by post and it appeared that the outer cover was nothing more than an advertisement by Allen & Hanburys. The views expressed in the articles were slanted very heavily towards its products. The complainant alleged that it was a poor reflection of the pharmaceutical industry.

*Response* Allen & Hanburys submitted that prior consultation with the Code of Practice Authority had not thrown up any concerns and this, combined with the fact that there were only two complaints out of 21,000 doctors mailed and as 1,947 doctors had requested a sample following the mailing, it was reasonable to assume that the vast majority had not been offended by the item. The company pointed out that the item was clearly marked "For The Medical Profession Only" and "Special Edition". Prescribing information for all the products mentioned was included. The Allen & Hanburys' logo was clearly marked. The item, was therefore, clearly a special advertising edition produced by the company. It was not disguised promotion.

*Ruling* The Panel noted that companies approaching the Code of Practice Authority for advice were aware that the Authority could only give informal guidance and would not approve any item. In this instance discussion had taken place; the Authority considered that potential concerns had been pointed out; Allen & Hanburys considered that the discussion had not thrown up any concerns.

The Panel noted that the item consisted of four pages set out in the style of the newspaper and that prescribing information was included. The Panel considered that the style and tone of the item failed to recognise the special nature of medicines and the professional standing of the recipients and ruled a breach of Clause 9.1 of the Code. The Panel noted that the statement "For The Medical Profession Only" appeared immediately below the title of the newspaper. It did not consider, however, that it was immediately apparent that the item was promotional. The Panel therefore ruled a breach of Clause 10.1 of the Code.

**Complaints received** **3 & 9 May 1994**

**Case completed** **10 June 1994**

## CASE AUTH/152/5/94

## GENERAL PRACTITIONER V CILAG LTD

### Conduct of a representative

*Complaint* A general practitioner, complained about the conduct of a representative from Ortho Cilag. Ortho Cilag sent him an advertisement with a tear off slip for a copy of a book "The Menopause and HRT". He had indicated that he would like a copy and had returned it to the company. In early April, one of the company's representatives had arrived in his surgery without an appointment with this book. Unfortunately, he was in the middle of a busy surgery and was unable to see her and asked her if she wished to leave the book she had brought. However she declined, saying that the book was very valuable and that she would only give it to the doctor in person and that she would be back later in the year. The complainant thought that most people would construe this representative's behaviour as using a 'gift' to gain access to a doctor to promote her company's product. Like most of his colleagues he was grateful for literature produced as a service to the medical profession. He abhorred it when it was used for other purposes.

*Response* Cilag Ltd accepted that its representative's conduct was easily interpretable as constituting an inducement to a further interview. Cilag insisted that this was not intentional but accepted that there had been a breach of Clause 15.3 of the Code. The representative had been reprimanded and a letter had been sent to all representatives reminding them of the importance of complying with the Code.

*Ruling* The Code of Practice Panel ruled that there had been a breach of Clause 15.3 of the Code as the representative had used the book as an inducement to gain an interview.

**Complaint received** **6 May 1994**

**Case completed** **23 May 1994**

## CASE AUTH/154/5/94

## GENERAL PRACTITIONER V LEDERLE LABORATORIES

### Misleading layout of a claim

*Complaint* A general practitioner complained about a mailing on Minocin MR (Ref: Mini 26 April 1994) sent by Lederle Laboratories. The mailing included the statement "One Minocin MR capsule costs 9p per day less than 2 x 50 mg Minocin"

The complainant alleged that the advertisement was misleading as at a quick glance the impression given was that the medicine cost 9p per day whereas the actual cost was 55p per day.

*Response* Lederle Laboratories stated that the mailing was sent to general practitioners to notify those who used Minocin 50 that the Minocin MR formulation was available at a saving of 9 pence per day over the original version of Minocin.

The company submitted that the statement was intended to be read in full. It made the point quite clearly that "One Minocin MR capsule costs 9p per day less than 2 x 50 mg Minocin"

*Panel's Ruling* The Panel examined the advertisement and noted that it had been laid out so that the statement "One Minocin MR capsule costs 9p per day" appeared on one line with "less than 2 x 50 mg Minocin" appearing immediately below. The Panel accepted that there might be some confusion if the claim was glanced at quickly. It considered, however, that it was not unreasonable to expect doctors to read the statement in full. It noted that the same typeface and style had been used for both lines. The Panel therefore ruled no breach of the Code.

*Appeal by Complainant* The complainant pointed out that mailings from pharmaceutical companies were only briefly glanced at and sometimes not completely removed from the envelope before being discarded into the wastepaper bin. In this specific case the large bold type was eye-catching and completely misled as to the cost of the medicine.

Lederle Laboratories did not submit any information for the appeal additional to that already submitted to the Panel.

*Appeal Board's Ruling* The Appeal Board noted the layout of the page in question:-

JUST THE ONE
One Minocin MR capsule costs 9p per day
less than 2 x 50mg Minocin.

The Appeal Board noted that although the claim was factually correct, its layout initially gave the impression that the product cost 9 pence per day. The layout of the claim was such that the cost of Minocin MR was not clear and the Appeal Board therefore ruled a breach of Clause 7.6 of the Code. The appeal therefore succeeded.

**Complaint Received 9 May 1994**

**Case Completed 17 August 1994**

**CASE AUTH/155/5/94**

**GENERAL PRACTITIONER V DU PONT PHARMACEUTICALS LIMITED:**

**Organisation of a meeting by a representative**

*Complaint* A general practitioner, complained about a hand-written invitation from a medical representative of Du Pont Pharmaceuticals Limited.

The invitation was headed "Defensive driving course" and referred to a series of defensive driving courses to be organised at the Exeter Driver Training Centre by the representative. The courses were to run from 9.45 am to 1.30 pm and were to consist of 45 minutes on each of the following:

a) skid-car
b) HGV experience
c) driver assessment
d) coffee/video/product talk

Each course was to be followed by a short talk on heart failure. Doctors were asked if they were interested in attending one of the courses which were to be held on 4 June, 11 June or 2 July and requested to sign the attached hand-written response form if they were.

In writing to Du Pont Pharmaceuticals Limited attention was drawn to the provisions of Clauses 2, 15.2, 18.1 and 19.1 of the Code.

*Response* Du Pont Pharmaceuticals Limited stated that the representative had established that a consultant geriatrician would be willing to speak on "ACE - inhibitors in general practice" subject to arranging suitable dates. The company submitted that this was an important and relevant topic for general practitioners given the recent licensing of ACE inhibitors for use in congestive heart failure in general practice. The speaker and topic were, of course, to be mentioned to the general practitioners. Those who decided to attend would have understood the primary purpose of the meeting was the promotion of the product and the relevant talk on heart failure.

The company submitted that offering training in defensive driving was appropriate, educational, inexpensive and relevant to the doctors' practice as an alternative to the normal promotional items which were generally handed out by the industry and were of rather less use. The company provided statistics to show how important driving skills were. The company's emphasis on training its own employees to a high standard of driving through defensive driving courses was well known. General practitioners clearly needed to drive as part of their work, sometimes in emergency situations and in bad weather and traffic conditions.

The company submitted that the letter was merely seeking information as to the interest of the doctors in the meeting and the suitability of certain dates prior to arranging any meeting. The company argued that the seeking of information as to the doctors interest in, and availability to attend meetings was normally done by industry representatives orally and no objection is raised to such activity. Since the meetings had not taken place, questions as to potential breaches of the Code were academic. It had however, instructed the representative not to proceed further with the organisation of this or similar meetings without discussion with the Authority.

Copies of the company's standard operating procedures were provided. The cost of the meeting would have been approximately £29 per head.

***Code of Practice Panel's Ruling*** The Panel noted that it was a well established principle that unacceptable offers of gifts or hospitality could be ruled in breach of the Code even if the offer had been withdrawn before anything had been provided. In this regard the Panel noted that Clause 18 of the 1993 Code referred to the offer of a gift, benefit in kind or financial inducement and that Clause 19 referred to the offer of hospitality. The arrangements were therefore subject to the Code.

The Panel noted that the Code applied to what representatives said as well as what was in writing. An oral invitation to an unacceptable meeting could be ruled in breach of the Code.

The Panel also noted that the letter from the representative stated "I am organising a series of defensive driving courses". The letter was making a clear offer rather than merely seeking information as submitted by the company. In any event, an enquiry about the interest of doctors in a proposed meeting was considered by the Panel to amount to an offer to arrange such a meeting.

The Panel considered that the overwhelming impression from the invitation was that the main purpose of the meeting was the defensive driving course with the educational content forming only a small proportion of the time. Although doctors would derive some benefit from training in defensive driving, the Panel considered that the course described in the invitation was predominantly for recreational purposes.

The Panel considered that offering such a meeting was unacceptable. The Panel therefore ruled a breach of Clause 19.1.

The Panel considered that by offering such a meeting the representative had not maintained a high standard of ethical conduct and therefore ruled a breach of Clause 15.2 of the Code.

The Panel considered whether the circumstances were such as to require the stronger censure of the ruling of a breach of Clause 2 of the Code but decided that this was not warranted as doctors would derive some relevant educational benefit.

**Complaint received** **19 May 1994**

**Case completed** **17 June 1994**

CASE AUTH/156/5/94
CASE AUTH/157/5/94
CASE AUTH/158/5/94

GENERAL PRACTITIONER V BRISTOL-MYERS SQUIBB PHARMACEUTICALS LTD, HOECHST UK LIMITED AND THE WELLCOME FOUNDATION LIMITED

Golf arranged by representatives

Complaint A general practitioner complained about a joint invitation to a day's golf which had been received from the local representatives of Bristol-Myers Squibb Pharmaceuticals Limited, Hoechst UK Limited and The Wellcome Foundation Limited. The invitation offered a half or a full day's golf on 27 May 1994 and stated that lunch and refreshments would of course be provided.

In writing to the companies concerned, attention was drawn to Clauses 2, 15.2, 18.1 and 19.1 of the Code.

*Responses* Bristol-Myers Squibb (Case AUTH/156/5/94) said that the letter written by its representative was inappropriate and clearly constituted a breach of Clause 19.1 and, therefore, presumably of 15.2. The representative concerned accepted that the letter was inappropriate but had advised that the letter did not accurately represent the arrangements for the day. The proposed format of the day was a discussion on ACE inhibition in heart failure and post myocardial infarction and the role of ACE inhibitors in these therapeutic areas. This was then to have been followed by a light sandwich luncheon. The representative had advised that it was his intention to invite a consultant cardiologist to speak on ACE inhibition.

Neither the regional manager nor Bristol-Myers Squibb Pharmaceuticals had approved the meeting or the invitation letter. It considered it to be a breach of company policy as well as of the Code of Practice and it had instituted disciplinary procedures.

The company did not believe that there had been a breach of Clause 2 because as soon as the letter was brought to its attention the meeting had been cancelled and disciplinary procedures put in place and because the letter was not on company headed paper and there was no mention of the company or its products.

Hoechst UK Limited (Case AUTH/157/5/94) stated that the association of its representative with the proposed meeting was unacceptable. The activity was against Hoechst standard procedures for

initiating meetings with doctors in which all proposals were scrutinised by regional and, where necessary, national managers, and in this case it did not happen. To proceed to a written communication, in such a situation without scrutiny and permission was also unacceptable to Hoechst. As a result of this and, of course, the ensuing complaint, the representative had already received a formal reprimand and would be the subject of admonishment and disciplinary action under Hoechst UK disciplinary procedures. The company asked, however, that consideration be given to a number of points in mitigation, both in relation to the meeting itself and its representative's involvement, so as to place the episode both in the correct context and in perspective.

Firstly, although it was not clear from the letter of invitation, the three companies were not involved in either paying for or organising the golf match itself. This activity was an attraction for general practitioners to come to a venue for a medical lecture and receive modest refreshments. Thus it was appropriate to consider the plans for the medical aspects for the day to be separate from the golf. The purpose of the meeting was for a new local consultant cardiologist to give a medical lecture to the general practitioners in attendance in an area of therapeutics of common interest to all participants. In these circumstances there would not have been much opportunity for any direct promotion or even company specific product promotion.

Secondly, the meeting would not take place. Whilst this fact itself did not lessen culpability related to intent, it did mean that much of the discussion regarding the intended events of the day were reduced to both supposition and conjecture.

Thirdly, while its representative's judgment could be questioned over this episode, his actual involvement seemed to have been peripheral. He did not sign the letter and Hoechst now knew that he did have concerns about its format and content. For this reason he did not post the letter directly to his own invitees but visited them in person to explain the nature of the event and its medical context, and to ensure that each of the attendees were members of the medical profession.

Hoechst made available copies of letters which had been submitted by the invited doctors on its representative's behalf, to confirm that they were under no illusion that the green fees would be paid for by the companies involved but that refreshments would be served. They had also confirmed that they were aware that a medical talk would be given at lunchtime.

The representative in question had been a senior medical representative with Hoechst Pharma for sixteen and a half years and there had been no cause to question his integrity and honesty or even foolishness. The company considered that it was a one off situation.

Hoechst did not believe that its representative's actions had breached Clauses 2, 15.2, 18.1 or 19.1 of the Code of Practice, although it did accept that the invitation to a proposed meeting did contravene paragraph 2 of Clause 15.3.

The Wellcome Foundation Ltd (Case AUTH/158/5/94) said that it had interviewed the representative concerned and he had explained the background of the event. It was clear that the representative did not obtain permission from his line manager, or anyone else in Wellcome, to arrange what he had agreed was a breach of the Code. Since all of its representatives had a full understanding of the Code and were aware that this formed part of their terms and conditions of employment there was no excuse for this breach. With this in mind the representative had been severely reprimanded.

Wellcome would not condone activities of this nature and sincerely regretted that this event was organised by an experienced representative with a previously clear record of some 26 years.

Wellcome would be reminding representatives of their obligation to both Wellcome and to the industry under the Code and would use this episode as an example to reinforce the importance of the Code.

*Ruling* The Code of Practice Panel observed that the letter of invitation had been signed by the representatives from Bristol-Myers Squibb and Wellcome but not by the representative from Hoechst, though it bore the latter's name. The letter was written from a private address and stated "We have much pleasure in inviting you to a days (sic) golf .....".

It was considered difficult to reconcile this with Hoechst's contention that the doctors invited were to pay their own green fees and organise the golf match themselves. The letters from four doctors which had been submitted by Hoechst were noted. These stated that they had known that they would pay their own green fees and that there would be an educational content. Neither Bristol-Myers Squibb nor Wellcome had submitted that the doctors were to pay their own green fees.

The Panel noted the supplementary information to Clause 19 of the Code that "Meetings organised for groups of doctors, other health professionals and/or for administrative staff in hospitals and health authorities and the like which are wholly or mainly of a social or sporting nature are unacceptable."

The Panel considered that the day which had been arranged was mainly of a social or sporting nature even though a lecture on a medical topic had apparently been planned, though the invitation was silent on this point. Equally, the letter of invitation was silent on the question of who was to pay the green fees, the commonsense interpretation of the letter being that the invitors would pay. The Panel considered that the arrangements were in breach of Clause 19.1 of the Code and that the representatives concerned had behaved unethically in breach of Clause 15.2. In the Panel's view, the arrangements were quite unacceptable and brought discredit upon the industry in breach of Clause 2. The fact that the event did not take place was irrelevant. The offer had been made.

In Case AUTH/156/5/94, the Panel ruled that Bristol-Myers Squibb Pharmaceuticals Limited was in breach of Clauses 2, 15.2 and 19.1 of the Code.

In Case AUTH/157/5/94, the Panel ruled that Hoechst UK Limited was in breach of Clauses 2, 15.2 and 19.1 of the Code. The points put forward in mitigation, in particular the question of payment of green fees, were not considered to justify a less severe ruling. The representative had clearly been associated with an unacceptable joint event.

In Case AUTH/158/5/94, the Panel ruled that The Wellcome Foundation Ltd was in breach of Clauses 2, 15.2 and 19.1 of the Code.

**Complaint received** **12 May 1994**

**Cases Completed**

| | |
|---|---|
| **AUTH/156/5/94** | **16 June 1994** |
| **AUTH/157/5/94** | **15 June 1994** |
| **AUTH/158/5/94** | **14 June 1994** |

CASE AUTH/159/5/94

CONSULTANT PHYSICIAN V RHÔNE-POULENC RORER LIMITED

Misleading price comparison

A consultant physician, submitted a complaint about a detail aid for Celectol (Ref: P6078) issued by Rhône-Poulenc Rorer Limited which he alleged was in breach of Clauses 7.2 and 7.3 of the Code.

1. Chart headed "Comparative cost per day of antihypertensive agents"

Complaint The complainant pointed out that the chart gave the price of atenolol as 25 pence per day whereas it was, in fact, 4.25 pence per day. The complainant also pointed out that the chart omitted to quote the price of bendrofluazide which cost 0.5 pence per day. The complainant accepted that the prices he quoted were for non-proprietary products as quoted in the British National Formulary, number 27, but this strengthened the argument that Rhône-Poulenc Rorer had been insufficiently scrupulous in its choice of data for presentation.

Response Rhône-Poulenc Rorer pointed out that the Code prohibited the use of brand names of other companies' products without prior permission. Therefore the generic names for the comparator products were shown in the chart. The company submitted that the source of the data in the chart was clearly referenced to MIMS which was a publication well known for providing pricing information on branded, not generic, products.

The company submitted that the list of comparators was not intended to be exhaustive and was provided so that doctors and pharmacists were able to put the cost of Celectol and some other widely used branded anti-hypertensives into perspective. The company's promotion of Celectol positioned it against other beta-blockers, ACE inhibitors and calcium channel blockers and these were the products selected for comparison. The company did not accept that the data was misleading or that it could not be substantiated.

Ruling The Code of Practice Panel noted that Clause 7.10 of the Code prohibited the use of other companies' brand names without prior permission. Companies therefore generally used generic names in promotional material.

The Panel noted that the reference to MIMS did not appear on the same page as the chart. A reference number was given with the details on the final page of the detail aid and not on the page in question. It was not clear that the prices given were the prices of branded products. The Panel did not accept that even if the reference to MIMS had appeared on the page in question, readers would have necessarily known that the prices referred to branded products.

The Panel accepted the submission from Rhône-Poulenc Rorer that it was reasonable to compare Celectol with other beta-blockers, ACE inhibitors and calcium channel blockers and that such comparisons need not include every single product on the market. The Panel considered, however, that in view of the heading to the chart "Comparative cost per day of antihypertensive agents", limiting the scope of the chart to beta-blockers, ACE inhibitors and calcium channel blockers was inadequate as other products, such as diuretics, were used to treat hypertension.

The Panel decided that the chart was misleading as it did not state that the prices quoted were for branded products and as the heading was inappropriate given the range of products listed. The Panel therefore ruled a breach of Clause 7.2 of the Code.

**2. Reference to Celectol being contra-indicated in patients with reversible airways obstruction.**

**Complaint** The complainant alleged that the detail aid, in dealing with patients who persisted in smoking, failed to make clear that Celectol was contra-indicated in patients with reversible airways obstruction. This important contra-indication was only mentioned in light type in the abbreviated prescribing information.

**Response** Rhône-Poulenc Rorer Limited pointed out that the prescribing information clearly stated that Celectol should not be given to patients with reversible airways obstruction. The company did not accept that the statement that Celectol might be given to patients who continued to smoke was in contravention of its data sheet. Clearly there would be some patients who continue, against medical advice, to smoke who did have reversible airways obstruction and to whom Celectol should not be given. However, for those hypertensive patients who smoked and did not have any degree of reversible airways obstruction, Celectol was not contra-indicated. The company was adamant that Celectol should not be promoted for use in patients with reversible obstructive airways disease.

**Ruling** The Panel noted that the data sheet for Celectol stated "Although cardioselective beta blockers may have less effect on lung function than non-selective beta blockers, as with all beta blockers these should be avoided in patients with reversible obstructive airways disease unless there are compelling clinical reasons for their use" and the prescribing information warned that Celectol was contra-indicated in patients with "reversible airways disease unless compelling reasons for use." The Panel noted that the contra-indication was not an absolute contra-indication. The contra-indication for beta blockers in patients with reversible airways obstruction was a class warning associated with all beta blockers.

The Panel considered that general practitioners would be aware of this warning prior to prescribing beta blockers. The Panel therefore ruled no breach of the Code.

**Complaint received** **16 May 1994**

**Case completed** **20 July 1994**

## CASE AUTH/160/5/94

## MARION MERRELL DOW V UCB PHARMA

### Promotion of Zirtek

Marion Merrell Dow Ltd complained about the promotion of Zirtek (cetirizine) by UCB Pharma Ltd. UCB Pharma although not a member of the ABPI had nevertheless agreed to comply with the Code.

The promotional material at issue was a fold out leaflet (ref: UCB 124). There were three matters of complaint which were considered as follows:

1. **A claim "Zirtek significantly more effective than terfenadine in hayfever"**

*Complaint* Marion Merrell Dow alleged that the claim did not reflect the balance of evidence in the scientific literature in breach of Clause 7.2. The company acknowledged that there might be

individual studies which supported the claim but the weight of the published evidence was that there was no significant difference between the two products as regards clinical efficacy.

*Response* UCB identified nine clinical studies which used the recommended 10mg dose of cetirizine. Cetirizine emerged as superior to terfenadine in four studies, was equal to terfenadine in four studies and one study showed that terfenadine was superior to cetirizine. The company drew particular attention to features of three studies.

*Ruling* The Panel examined the studies provided and made a number of criticisms. The Panel considered that the claim "Zirtek significantly more effective than terfenadine in hayfever" did not reflect the balance of the evidence as although one study showed a statistically significant difference, some studies showed no difference between the products and one showed a statistically significant difference in favour of terfenadine. The Panel ruled a breach of Clause 7.2 of the Code.

2. Statement "... should be the antihistamine of first choice"

*Complaint* Marion Merrell Dow alleged that the statement included the use of a superlative in breach of Clause 7.8.

*Response* UCB Pharma submitted that the statement was a quote taken from a review of published data on antihistamines. The company accepted the significance of the supplementary information to Clauses 11.1 and 7.8 of the Code and had therefore removed the statement from its new literature.

*Ruling* The Panel noted that the complete statement was "Based on published literature Zirtek should be the antihistamine of first choice. "First" was not a superlative as defined in the supplementary information to Clause 7.8 of the Code. It was considered, however, that the statement implied a superiority for Zirtek which in view of its ruling in point 1 above was not borne out by the available evidence. The Panel therefore ruled a breach of Clause 7.8 of the Code.

3. Graph appearing beneath the claim "Zirtek significantly more effective that terfenadine in hayfever"

*Complaint* Marion Merrell Dow pointed out that the graph which compared terfenadine with Zirtek had a suppressed zero on the vertical axis and alleged that the graph was in breach of Clause 7.6 of the Code.

The graph showed mean total severity of symptoms against days and indicated that there was a statistically significant difference in favour of Zirtek on days 5 and 7.

*Response* UCB acknowledged the significance of the supplementary information to Clause 7.6 of the Code and advised that it had amended the graph in its new literature.

*Ruling* The Panel considered that there might be occasions when it was possible to use a graph with a suppressed zero. Such graphs were not ruled out per se.

The Panel considered, however, that in this instance the use of the suppressed zero exaggerated differences between the products even though the graph had been annotated to show on which days there were statistically significant differences between the products. The visual impression of the graph was that there was a large difference between the products and if the graph had been drawn without a suppressed zero this difference would not have been so marked. The Panel considered that the graph was misleading and ruled a breach Clause 7.6 of the Code.

**Complaint received** **16 May 1994**

**Case completed** **6 July 1994**

CASE AUTH/161/5/94

PHARMACEUTICAL OFFICER TO A FAMILY HEALTH SERVICE AUTHORITY V MEMBER COMPANY

Journal advertisements

*Complaint* A pharmaceutical officer with a family health service authority complained about two advertisements issued by a member company for one of its products.

The complainant alleged that the nature of the advertisements seemed to suggest that those who intended to partake in a particular activity were at risk of acquiring a particular condition for which the product in question was used. The complainant alleged that this was scaremongering and entirely inappropriate and out of line with current recommended guidelines. The complainant alleged that the intention of the advertisements was to induce clinicians to prescribe the product inappropriately.

*Response* The company provided detailed information about the recommendations regarding the use of the product.

*Ruling* The Code of Practice Panel decided that the advertisements were not unacceptable given the recommendations on the matter and therefore ruled no breach of the Code.

**Complaint received** **20 May 1994**

**Case completed** **29 June 1994**

CASE AUTH/162/5/94

DRUG REVIEW COMMITTEE V MEMBER COMPANY

Letter to unit general manager

*Complaint* A chief pharmacist complained on behalf of a drug review committee at a NHS Trust hospital about a letter sent to the unit general manager by a member company announcing the launch of a new product. The letter provided brief details about the product and claimed that certain savings would be made to the NHS drugs bill if they changed to prescribing the new product.

The complainant queried the provision of prescribing information in the letter which he considered was not relevant to non-clinical managers. The complainant also alleged that the financial information given in the letter, although perhaps more relevant, was inaccurate and misleading with regard to the local situation.

*Response* The company pointed out that it was its understanding that prescribing information was required when sending information to administrative staff. Whilst competitor products might be obtained at discount at the complainant hospital, the complainant must realise that 95% of prescribing was carried out by general practitioners.

*Ruling* The Panel noted that it was well established under the Code of Practice that the promotion of medicines to administrative staff in hospitals etc was not unacceptable providing that certain requirements were observed as referred to in the supplementary information to Clause 1.1 of the Code. These included the need to include prescribing information on such material distributed to administrative staff and the need to ensure that it was appropriate for its recipients.

The Panel ruled there was no breach with regard to the allegation concerning the inclusion of prescribing information on the letter and considered that the letter was not inappropriate for its recipients.

With regard to the second matter, the Panel noted that different hospital purchasing units might obtain discounts on medicines with discounts varying between different units and purchases over time. It would not be possible to take account of all local variations in calculating global figures based on projected sales even if all of the financial information was available.

The Panel acknowledged that the actual differences in costs resulting from switching to the advertised product might not be those projected in the letter. It considered, however, that it was apparent from the information presented in the letter that the proposed cost savings were based on a straightforward calculation of NHS list prices for the products and projected sales figures. As such, it drew the recipient's attention to the possibility of cost savings.

The Panel considered that the presentation of the financial information in the letter was not unacceptable and ruled there was no breach of the Code.

**Complaint received** **23 May 1994**

**Case completed** **20 June 1994**

**CASE AUTH/164/6/94**

**HEALTH PROFESSIONAL IN A HOSPITAL V MEMBER COMPANY**

**Meeting on a research programme**

*Complaint* A health professional in a hospital complained about a meeting held by a member company. The complainant stated that the product mentioned was not currently licensed in the UK. The meeting had been attended by surgeons, anaesthetists, cardiologists and pharmacists and had consisted of a senior medical adviser of the company giving a slide show. The talk emphasised the discovery of the product, its use in animal trials and the results of Phase III clinical trials. At no point was the cost of the product mentioned. There was a session at the end for questions.

*Response* The company concerned said that during the clinical development of the product it had sought and received advice from the scientific community with regard to the interpretation of pre-clinical and clinical work as well as areas of research which were to be addressed further. On occasion, a member of the company's scientific team had been invited to speak on the concept of the product and the research programme. A standardised slide set was selected and had been used in all presentations.

A copy of the content of the slides was presented.

The company submitted that the meeting in question took place after an invitation from a member of staff in the hospital concerned and was not organised or initiated by the company. The company refunded the cost of light refreshments only. The presentation made it clear that the product was not licensed or available for clinical use. The meeting was a legitimate exchange of medical and scientific information concerning the development of future medicines.

Literature on one of the company's licensed products had been displayed.

*Panel's ruling* The Panel noted that the meeting had been arranged by a member of staff at the hospital. The Panel considered that the meeting was a genuine scientific/educational meeting. In this regard, the Panel noted that the presentation had been given by a senior clinical research physician, it had been stated that the product was still undergoing clinical development and had not yet been licensed and no literature concerning it was either displayed or offered. It also noted that the company had only provided light refreshments for the meeting, no other payments having been made.

The Panel referred to the supplementary information to Clause 3 that

> "The legitimate exchange of medical and scientific information during the development of a medicine is not prohibited provided that any such information or activity does not constitute promotion which is prohibited under this or any other Clause".

The Panel considered that the meeting did not constitute promotion and therefore ruled no breach of Clause 3 of the Code.

**Complaint received** **2 June 1994**

**Case completed** **5 July 1994**

## CASE AUTH/167/6/94

## MONMOUTH PHARMACEUTICALS LIMITED V MEMBER COMPANY

### Imitation of slogan

*Complaint* Monmouth Pharmaceuticals Limited, a company not in membership of the ABPI, alleged that the use of a slogan in advertisements issued by a member company for one of its products was in breach of Clause 9.3 of the Code. Monmouth had been promoting one of its own products for over a year with a similar slogan. Monmouth considered that the slogan in the advertisements imitated its own slogan in a way that was likely to mislead or confuse doctors. There was a real possibility that this might mislead some doctors into thinking that the two products were the same or it might lead to confusion between them.

*Response* The company said that phrases such as that at issue were common parlance. An on-line search of the texts of daily newspapers over the last twelve months identified 639 references to similar phrases. A print-out of the twenty more recent uses from the last 17 days was provided as examples. It followed therefore that the use of a common everyday phrase in its promotion could not be regarded as copying the slogan which Monmouth implied was unique to its advertising. Since

it was a phrase in common usage it was unlikely to mislead or confuse. The advertisements showed no similiarity with regard to general layout, colour and visualisation.

*Panel Ruling* The Code of Practice Panel noted that Clause 9.3 stated "Promotional material must not imitate the devices, copy slogans or general layout adopted by other companies in a way that is likely to mislead or confuse". Although there was similarity of wording between the two advertisements, the Panel considered that the expressions involved were in common usage. The visual devices were completely different. The Panel did not consider that the usage of the slogan was such as to be likely to mislead or confuse. The Panel ruled that there had been no breach of the Code.

**Complaint received** **15 June 1994**

**Case completed** **13 July 1994**

CASE AUTH/168/6/94

DOCTOR v ROCHE PRODUCTS LIMITED

Bioavailability claim in journal advertisement

*Complaint* A doctor alleged that a claim "After intramuscular injection 90% of peak plasma concentration is achieved in 15 minutes" which appeared in an advertisement for Mobiflex Vials in the 12 March 1994 issue of the British Medical Journal (Clinical Research edition) was incorrect and misleading.

The complainant alleged that the claim was unqualified suggesting that 90% of peak plasma concentration was reached in the time in all subjects investigated and that this was likely to happen in all patients. On requesting the data on file, to which the claim was referenced, the complainant had received a summary of a research report by Guntert *et al* which stated that 90% of peak plasma concentration was achieved in 10 out of the 12 administrations in the study. Furthermore, the study was done in healthy volunteers and absorption was likely to be slower in many patients with musculoskeletal disorders who moved less.

*Response* Roche Products Limited stated that the point of doing studies in groups of volunteers or patients was to investigate a sample of a population to provide an estimate of the performance of that population. In such studies, the individual results were pooled to provide such an estimate. It could not be assumed that any of the individuals who participated, particularly the outliers, would always perform as they did on a single occasion, so the means or averages from groups of 10 or 12 volunteers were used to predict the performance of the whole population. In the Guntert study, the mean of the individual peak plasma concentrations was calculated in two ways and in each case the mean of the individual plasma levels at 15 minutes was greater than 90%. Moreover, the claim in the advertisement was consistent with the statement in the data sheet for the product that "Following intramuscular injections levels at or above 90% of the maximally achieved concentrations are reached as early as 15 minutes after a dose...".

Finally, with regard to the complainant's assertion relating to the study being in healthy volunteers whereas many patients with musculoskeletal disorders would move less, the company pointed out that the protocol for the Guntert study recognised this potential source of error and required the test subjects to remain sitting down or recumbent for the first two hours after medication.

Copies of the full report on the Guntert study were submitted.

*Ruling* The Panel accepted the assertion made by the complainant that the claim "After intramuscular injections 90% of peak plasma concentration is achieved in 15 minutes" implied that 90% of peak plasma concentration was achieved within 15 minutes in all subjects investigated and considered that the results of the Guntert study did not show this. Further, the claim in the advertisement did not refer to the fact that the results were obtained in healthy volunteers. Although account had been taken of this in the study by requiring test subjects to remain sitting down or recumbent for two hours after medication, it was an established principle under the Code that any claim in advertising was automatically read as referring to data in patients and that if this was not the case, the position had to be made clear in the advertisement.

The Panel did not accept the company's submission that the claim in the advertisement was consistent with a statement in the data sheet regarding the achievement of 90% of peak plasma concentration in 15 minutes. The Panel noted that both the statement in the pharmacokinetics section of the data sheet and the statement appearing in the summary in the Guntert study were qualified by the words "as early as", which implied that not all reached 90% maximal concentration within fifteen minutes after dosage. This qualification did not appear in the claim in the advertisement.

The Panel considered that the claim in the advertisement was not a clear reflection of the data and ruled a breach of Clause 7.2 of the Code.

**Complaint Received** **17 June 1994**

**Case Completed** **13 July 1994**

**AUTH/170/6/94**

**FHSA PHARMACEUTICAL ADVISER - v - MEMBER COMPANY:**

**Alleged excessive inducements**

*Complaint* A complaint was submitted on behalf of the pharmaceutical adviser to a family health service authority about the promotion of a product by an ABPI member company. The complaint arose from an article in a journal which referred to services which were offered in connection with its supply. These included discounts, the facility to return unused products and the services of a health professional to assist with its use. It was alleged that the inducement was excessive.

When writing to the company, attention was drawn to Clause 18 of the Code.

*Response* The company said that the article in question was not prepared by the company nor did it have any editorial control. The article was inaccurate and exaggerated the true case. The company argued therefore that the complaint should not fall within the scope of the Code.

The article roughly reflected a sales scheme which operated under the general heading "terms of trade", whereby preferential services, such as discounts, were offered depending on order value. Such services had commonly been applied in this product area. In addition to or in place of discounts, the scheme offered advice and help, the ability to return unused stock and limited help from a health professional. Although the scheme operated under terms of trade, the company believed that even if its actions were considered to be promotional, they were fully in line with Clause 18.1 of the Code by providing a medical service of benefit to both patient care and the

National Health Service.

*Ruling* The Panel did not accept the company's contention that because the article was inaccurate, the complaint did not fall within the scope of Code. It considered that the complaint was quite clear and did not fail merely because the article upon which it was based was inaccurate. Further, the Panel did not accept that the services provided could be regarded as the provision of medical and educational goods and services which would enhance patient care or benefit the National Health Service as referred to in the supplementary information to Clause 18.1. This exception to the provisions of Clause 18.1 only applied when goods and services were provided in such a way as not to be an inducement to prescribe, supply, administer or buy any medicine. This was clearly not the case here.

The Panel noted that the 1993 edition of the Code excluded from its requirements "terms of trade". The 1994 edition excluded "measures or trade practices relating to prices, margins or discounts which were in existence on 1 January 1993".

The Panel noted that discounts and the like had previously been ruled to be acceptable but it had been noted that they might in some circumstances be viewed as an attempt to influence the prescribing decision of a doctor. This could particularly be a potential problem in relation to dispensing doctors, where a doctor was not only prescribing in a professional capacity but was in fact also buying the medicines. The same applied to some products in relation to both dispensing and non-dispensing doctors. Clearly there were circumstances when terms of trade might be such as to be unacceptable, as unreasonably influencing the prescribing decisions of doctors. These would be prohibited under Clause 18 of the Code.

The Panel considered that although the offer of services in connection with the supply of a product could clearly be viewed as being an inducement to prescribe, supply or administer it, companies should not be precluded from offering services as part of a package relating to the supply of a medicine as long as they were reasonable. In the present case, the Panel considered that the scheme was a package deal. That was to say that those were the terms under which the product was supplied and doctors could accept them or not as they chose. The benefits were directed towards the doctors' practices and were business benefits and not personal benefits, such as items which could be used in the home. It was considered that this particular scheme was reasonable in nature and not unacceptable and it was ruled that there was no breach of the Code.

**Complaint received** **20 June 1994**

**Case completed** **27 July 1994**

CASE AUTH/171/6/94

MEDICAL ADVISER TO A FAMILY HEALTH SERVICES AUTHORITY V NON MEMBER COMPANY

Reference details omitted from a mailing

*Complaint* A medical adviser to a family health services authority complained about a mailing sent by a non member company. The complainant pointed out that two reference numbers were given in the mailing although the text did not give any source for the references.

*Response* The company concerned, although not a member of the ABPI, had nevertheless

agreed to comply with the Code. The company apologised for the omission of the references on the mailing which was a regrettable oversight. The references should have appeared on the back page. Unfortunately, during production the line bearing the references was omitted and not identified on checking. Any doctor who asked for the references would, of course, be supplied with the original papers. The references were quoted elsewhere on other items of promotional literature.

*Ruling* The Panel noted a previous case, Case COP/1161/11/92 which had concerned the omission of references cited in a "Dear Doctor" letter. In that case it had not been accepted that omission of details of the references cited in the mailing was a breach of the Code and it had therefore been ruled that there was no breach of the Code.

The Panel noted that the requirements of the Code for references had changed since the decision in Case COP/1161/11/92 as Clause 7.5 stipulated that, when promotional material referred to published studies, clear references must be given. The Panel noted that in this instance the referenced claims did not constitute references to published studies as such and therefore Clause 7.5 of the Code did not apply.

The Panel decided that the omission of the source of the references cited in the mailing was not in breach of the Code and therefore ruled that there was no breach of the Code.

**Complaint Received 22 June 1994**

**Case Completed 8 July 1994**

CASE AUTH/176/7/94

GENERAL PRACTITIONER V NON MEMBER COMPANY

Mailing to practice managers

*Complaint* A general practitioner complained about a mailing sent by a company not in membership of the ABPI which had agreed to comply with the Code. The mailing was sent to the practice manager and discussed possible savings to the NHS if doctors were to prescribe certain named products instead of other branded versions of the same products. The mailing consisted of a letter to the practice manager together with a copy of a brochure and the "Dear Doctor" letter with data sheets which had announced the introduction of the new product.

The complainant stated that although it was appreciated that the material was sent to the practice manager as promoting a business advantage, the practice felt very strongly that this sort of action was neither necessary nor ethical even though the actual letter to the practice manager was carefully worded. The practice considered that it would be quite sufficient for the company to point out potential cost savings to the doctors and for the doctors to ask, if they so wished, for the practice manager to work out figures for the practice. It was considered that it was very wrong for the practice manager to be approached directly by the pharmaceutical company for this purpose.

*Response* The company submitted that the products named had been introduced earlier in the year with data sheets and a covering letter sent to all general practitioners. This was the letter also included in the mailing. The objective of the mailing was simply to suggest that the practice manager bring the potential cost savings to the attention of doctors in the practice who might have missed the original mailing. Practice managers, in the company's view, were appropriate administrative staff as referred to under the Code as being a legitimate audience for promotion and information on

medicines and it could be reasonably assumed that they would have an interest in bringing opportunities for saving prescribing costs to the attention of their general practitioner colleagues. There were a growing number of branded products which were promoted exclusively on the basis of cost savings and this was acceptable. The content of the mailing had been carefully limited to cost issues with no attempt made to promote the clinical benefits of either product.

*Ruling* The Code of Practice Panel referred to the provisions of Clause 1.1 and its supplementary information on promotion to administrative staff. The Code recognised that it was legitimate to promote medicines to appropriate administrative staff as long as certain requirements were observed. These included the need to ensure that the material was appropriate to those to whom it was addressed (Clause 12.1). It was therefore acceptable in principle to send a mailing to practice managers.

The Panel considered that the content of the mailing was appropriate for the audience to whom it was addressed as it was concerned with potential cost savings which would be both of interest and relevant to practice managers. The Panel therefore considered that the mailing was not unacceptable and ruled there was no breach of the Code.

**Complaint Received** **11 July 1994**

**Case Completed** **4 August 1994**

CASE AUTH/179/7/94

DIRECTOR V MEMBER COMPANY

Apparent failure to implement undertaking

*Complaint* A previous case before the Code of Practice Panel concerned a journal advertisement issued by a member company for one of its products which was ruled in breach of the Code. The Code of Practice Authority noted that the advertisement at issue in this case appeared again in a subsequent edition of the same medical journal.

In accordance with guidance issued by the Code of Practice Appeal Board that a breach of an undertaking should be treated as a fresh case, the matter was taken up with the company concerned with reference being made to the original complaint. In addition, the company was advised that Clause 2 was now relevant because of the apparent failure to comply with the previous undertaking.

*Response* The company had been assured by the journal that the UK edition carried the UK advertisement which complied with the Code and not the advertisement sent to the company by the Authority which was the international advertisement. The company submitted that it appeared the international edition of the journal had been provided to the ABPI in error. The ABPI was the only organisation in the country to have seen the international edition of the journal. All UK subscribers received the UK edition.

*Panel Ruling* The Panel noted that the international edition of the journal had come to the ABPI as the result of an error on the part of the journal. This had been loaned to the Authority by the ABPI library. The Panel observed that there was no way of telling that it had been the international edition. The Panel accepted that the advertisement in question had appeared only in the international edition of the journal and not in the UK edition. The Panel therefore ruled that there was no breach of the Code.

**Complaint proceedings commenced** **19 July 1994**

**Case completed** **28 July 1994**

CASE AUTH/182/7/94

CONSULTANT ANAESTHETIST V ROCHE PRODUCTS LIMITED

Distribution and content of a leaflet alleged to be inappropriate

*Complaint* A consultant anaesthetist, submitted a complaint about a leaflet (Ref No: PO55318)on Mobiflex Vials issued by Roche Products Limited.

The complainant alleged that the leaflet, which was distributed as a loose insert with the British Journal of Anaesthesia, did not give a clear, fair and balanced view of the matters with which it dealt. The complainant drew attention to a single statement that Mobiflex produced a marked reduction in pain in patients suffering from low back pain which indicated that Mobiflex was not licensed for use in acute post operative pain. The distribution of the leaflet was to anaesthetists who dealt with patients in pain generally after operations and were much less likely to be dealing with patients for whom the product was licensed. The complainant alleged a breach of Clause 7.2 of the Code and, as the distribution was inappropriate, a breach of Clause 12.1 of the Code.

The complainant also referred to two instances, one in Edinburgh and one in Leicester, where the representatives promoting the product suggested that it could be used in patients with pain after operations. The entire tenor of the advertising campaign was that the product was an effective analgesic.

*Response* Roche Products Limited stated that the item in question was a leavepiece and was never used as a loose insert in the British Journal of Anaesthesia. It did, however, form part of a separate mailing to anaesthetists in January 1994 and an advertisement for Mobiflex Vials had been appearing in the British Journal of Anaesthesia. The company did not wish to offer any defence to the allegation that it had broken Clause 12.1 of the Code. A copy of a letter from the British Journal of Anaesthesia confirming the company's submission was provided.

The company referred to a recent Case AUTH/168/6/94 in which the company had been ruled in breach of Clause 7.2 of the Code with regard to the claim for Mobiflex Vials that "After intramuscular injections 90% of peak plasma concentration is achieved in 15 minutes" which also appeared in the leavepiece in question in this case.

The company submitted that the leavepiece was also used by representatives in interviews with physicians. The representatives in Edinburgh and Leicester had been interviewed and had denied having promoted Mobiflex for post operative pain and where the indication had been raised it was made clear that the indication was not licensed. Following the Panel's ruling in Case AUTH/168/6/94, the entire Mobiflex Vial campaign had been terminated.

*Ruling* The Code of Practice Panel examined the leavepiece and noted that the opening claim was "Give pain the push" which it considered was too general a claim for pain relief given that Mobiflex Vials was licensed only for the relief of pain and inflammation in osteoarthritis and rheumatoid arthritis. The Panel considered that it would not be sufficiently clear to anaesthetists receiving the leavepiece that the product was only licensed for the relief of pain and inflammation

in osteoarthritis and rheumatoid arthritis even though this information appeared in the prescribing information in the leavepiece. Given that the audience would be interested in the relief of pain post operatively rather that the relief of pain in osteoarthritis and rheumatoid arthritis, the Panel decided that the leavepiece was misleading. The Panel therefore ruled a breach of Clause 7.2 of the Code.

The Panel considered that the distribution of the leavepiece to anaesthetists was in breach of Clause 12.1 of the Code which required that promotional material should only be distributed to those categories of persons whose need for or interest in the particular information could reasonable be assumed. The Panel therefore ruled a breach of Clause 12.1.

With regard to the allegation concerning the representatives, the Panel decided in the absence of any evidence that there was no breach of the Code.

**Complaint Received** **20 July 1994**

**Case Completed** **10 August 1994**

CASE AUTH/183/7/94

DRUG INFORMATION PHARMACIST V DUMEX LIMITED

Promotion inconsistent with product licence

*Complaint* A drug information pharmacist complained about the promotion of Diazemuls injectable by Dumex Limited. Dumex was not a member of the ABPI and had not formally agreed to comply with the Code but it was understood that it was its intention to do so.

A Dumex representative had left a brochure which advised that Diazemuls could be administered by intramuscular and intravenous injection. The data sheet advised only of intravenous use. The complainant had queried intramuscular administration with the representative who was aware that this was an unlicensed use and as such he could not advise it officially. He had, however, left the literature. The complainant contacted the company which referred the enquiry to its head office in Denmark. The Danish medical information department was unconcerned about the UK Code and was unaware of the ABPI. The complainant had asked them to let her know what they were doing about withdrawing the item but had heard nothing.

*Response* Dumex said that the representative had discussed Diazemuls with the complainant and had agreed that intramuscular use was unlicensed in the UK. It was licensed in other European countries. The representative had agreed to supply data on intramuscular use via medical information. The line manager had been contacted by the representative and the error in the brochure had been noted. All sales representatives were informed of the error and instructed that a correction would be made and within five days a correction sticker had been provided and attached to all printed promotional material. An example was provided.

The company submitted that the error had occurred because the promotional material was based on an international product monograph which had intramuscular use as an indication. There had been no deliberate attempt to mislead clinicians or pharmacists by promoting the product other than in accordance with Clause 3.2 of the Code of Practice. The Danish medical information department had agreed with the complainant that intramuscular use was not indicated in the UK and that to promote the product in this way would be inappropriate. When the clinical data requested for the complainant was available, the representative would offer the corrected printed material. The company accepted that the

complainant could have received a more prompt response advising of the company's action and for this lack of expediency it apologised.

*Ruling* The Code of Practice Panel examined the brochure and noted that references to intramuscular use appeared on three pages. The correction which had subsequently been added to the inside front cover said "Erratum Page 4: The UK product licence does not include i.m. use". The Panel considered that the brochure was clearly promoting an unlicensed method of administration and ruled that there had been a breach of Clause 3.2 of the Code.

The Panel considered that the correction which had subsequently been added was totally inadequate. An error appearing in the body of a brochure could not be cured by a correction appearing inside the front cover. Use of the brochure would have to be discontinued unless it were possible to completely cover all references to intramuscular use by irremovable overstickers.

It was not clear what the representative had said about intramuscular use but Dumex should be reminded that it was contrary to Clause 3.2 for representatives to promote a product other than in accordance with the relevant product licence.

**Complaint received** **21 July 1994**

Case completed **11 August 1994**

CASE AUTH/188/7/94

MEDICINES CONTROL AGENCY V SMITH & NEPHEW

Campaign for District Nurses

*Complaint* The Medicines Control Agency (MCA) referred to the Authority a complaint it had received concerning the promotion of Bactigras by Smith & Nephew. The MCA considered that there might have been a breach of Clause 18 of the Code.

The material in question was a brochure which provided details of the Smith & Nephew "First Choice" campaign. The company was offering district nurses the opportunity to earn medical instruments and accessories by collecting "First Choice points". Various Smith & Nephew dressings had been allocated a points value and district nurses were urged to send in their points claims monthly together with proof of usage of particular Smith & Nephew dressings. Points could be traded in for various items of medical equipment ranging from a doppler to a first aid kit.

*Response* Smith & Nephew Healthcare Limited explained that Bactigras, one of the dressings mentioned in the brochure, had been sold by a separate division of the company, Smith & Nephew Medical. This division had been responsible for the marketing of all dressing products, the majority of which contained no active ingredient. The two companies had separate systems for approval of promotional material. Bactigras had a product licence.

Smith & Nephew acknowledged that the promotion of Bactigras was in breach of the Code and stated that if the promotion had been subject to the procedures at Smith & Nephew Pharmaceuticals, it would not have been approved. All copies of the brochure were being recalled from the sales force immediately and it would ensure that no licensed products were included in any such promotions in the future.

*Panel Ruling* The Code of Practice Panel noted that the relevant edition of the Code was the January 1993 edition as the promotion had been in place before 1 September 1994 and therefore

the transitional provisions in the 1994 edition of the Code meant that the complaint should be considered under the 1 January 1993 edition of the Code.

The Panel considered that the promotion of Bactigras was subject to the Code as the product was a medicine as defined under Clause 1.3 of the Code.

The Panel considered that the offer of the goods constituted the offer of unacceptable gifts as the offer was directly linked to sales of the products. The gifts could not be considered as promotional aids as they were not inexpensive. The Panel noted the requirements of Clause 18.1 of the Code, that no gift, benefit in kind or financial inducement shall be offered or given to members of the health professions for the purposes of sales promotion. The Panel therefore ruled a breach of Clause 18.1 of the Code.

The Panel considered that the "First Choice" scheme would also have been in breach of Clause 18.1 of the 1994 edition of the Code as the new supplementary information to that Clause only allowed the provision of medical and educational goods and services in a way which was not an inducement to prescribe, supply, administer or buy any medicine.

**Complaint received** **26 July 1994**

**Case completed** **19 August 1994.**

## CODE OF PRACTICE FOR THE PHARMACEUTICAL INDUSTRY

| NUMBER | | SUBJECT | BREACH |
|---|---|---|---|
| 89 | Astra v Allen & Hanburys | Letter to nurses | 7.2 (A) |
| 97 | Consultant Physician v Member Company | Prelaunch brochure | NoB (A) |
| 100 | Allen & Hanburys v Astra | Detail aid & letter | 7.2, 11.2 (A) |
| 116 | Allen & Hanburys v Member Company | Printed promotional material | NoB (A) |
| 117 | Allen & Hanburys v Member Company | Printed promotional material | NoB (A) |
| 120 | Baker Norton v Allen & Hanburys | Journal advertisements & letters | 7.2 (A) |
| 136 | B Braun v Non-Member Company | Journal advertisement | NoB |
| 138 | SmithKline Beecham v Wellcome | Observational study | 10.2, 18.1 (A) |
| 140 | Wellcome v SmithKline Beecham | Various promotional items | 7.2 |
| 142 | Wellcome v SmithKline Beecham | Various promotional items | 7.2 |
| 144 | Wellcome v Member Company | Booklet distributed at international meeting | Outside the scope of the Code |
| 145 | Director of Pharmacy Services v Member Company | Journal advertisement | NoB |
| 146 | Wellcome v SmithKline Beecham | Product monograph & another document | 4.1, 7.2 |
| 147 | Zeneca v Vestar | Printed promotional material | 7.2, 7.7, 11.2 |

| NUMBER | | SUBJECT | BREACH |
|---|---|---|---|
| 148 | Wellcome v SmithKline Beecham | Press materials | 7.2, 7.8 |
| 149 | SmithKline Beecham v Wellcome | Detail aid, mailing & journal advertisements | 7.2, 7.3, 7.7 (A) |
| 150 | Director v Member Company | Article in a publication | NoB |
| 151)<br>153) | General Practitioners v Allen & Hanburys | Outer cover of a newspaper | 9.1, 10.1 |
| 152 | General Practitioner v Cilag | Conduct of a representative | 15.3 |
| 154 | General Practitioner v Lederle | Mailing | 7.6 (A) |
| 155 | General Practitioner v Du Pont | Defensive driving course | 15.2, 19.1 |
| 156<br>157<br>158 | General Practitioner v Bristol Myers Squibb<br>v Hoechst<br>v Wellcome | Golf | 2, 15.2, 19.1 |
| 159 | Hospital Consultant v Rhône-Poulenc Rorer | Detail Aid | 7.2 |
| 160 | Marion Merrell Dow v UCB Pharma | Leaflet | 7.2, 7.6, 7.8 |
| 161 | Pharmaceutical Officer v Member Company | Journal advertisements | NoB |
| 162 | Drug Review Committee v Member Company | Letter to unit general managers | NoB |
| 164 | Health Professional v Member Company | Meeting | NoB |
| 167 | Monmouth v Member Company | Journal advertisement | NoB |
| 168 | Doctor v Roche | Journal advertisement | 7.2 |

| NUMBER | | SUBJECT | BREACH |
|---|---|---|---|
| 170 | FHSA Pharmaceutical Advisor v Member Company | Services offered with a supply of a medicine | NoB |
| 171 | Medical Adviser to FHSA v Non Member Company | Mailing | NoB |
| 176 | General Practitioner v Non Member Company | Letter to practice manager | NoB |
| 179 | Director v Member Company | Journal advertisement | NoB |
| 182 | Hospital Consultant v Roche | Leaflet | 7.2, 12.1 |
| 183 | Drug Information Pharmacist v Dumex | Brochure | 3.2 |
| 188 | MCA v Smith & Nephew | Brochure | 18.1 |

KEY

(A) Appeal
NoB No breach Numbers indicate clauses breached.