

CODE OF PRACTICE REVIEW

NUMBER 32

MAY 2001

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

Revised Code of Practice agreed by ABPI member companies

At the Annual General Meeting of The Association of the British Pharmaceutical Industry (ABPI) on 5 April, member companies agreed a revised version of the Code of Practice for the Pharmaceutical Industry. The new Code will come into operation on 1 July but, during the period 1 July to 30 September inclusive, no promotional material or activity will be regarded as being in breach of the Code if it fails to comply with its provisions only

because of requirements newly introduced.

Also agreed was a revised version of the Constitution and Procedure for the Prescription Medicines Code of Practice Authority. This will apply to complaints received on and after 1 July.

The main changes to the Code and the Constitution and Procedure are set out below. Full details have been sent to the chief executives of ABPI

member companies and those companies which though not ABPI members have agreed to comply with the Code and accept the jurisdiction of the Authority.

Printed copies of the new Code are now available and copies already ordered will be dispatched in June. A copy has been sent to everyone on the mailing list for the Code of Practice Review. Further copies are available on request.

Changes to the Code of Practice

The following are the main changes to the Code of Practice:

- the exclusion from the Code by Clause 1.1 of factual announcements and price lists etc which include no product claims will apply only to licensed medicines.
- the supplementary information to Clause 3 relating to promotion at international conferences has been revised and augmented.
- the supplementary information to Clause 3.1 relating to advance notification of new products has been amended and a requirement

added that such information must make clear whether the new medicine or the change to an existing medicine is the subject of a marketing authorization in the UK.

- added to Clause 4.1 is a requirement that prescribing information must be positioned for ease of reference and must not, for example, be placed diagonally or around the page borders.
- added to the supplementary information to Clause 4 is information relating to what is the most prominent display of the brand name in advertisements in electronic journals and information

about the provision of prescribing information on the Internet, including advertisements in electronic journals.

- in Clauses 4 and 5, the size of the non-proprietary name to be adjacent to the most prominent display of the brand name changes from 10 point bold to bold type of a size such that a lower case "x" is no less than 2mm in height.
- in Clause 5, it is made clear that abbreviated advertisements are not permitted in audio-visual material

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Changes to the Code of Practice *Continued*

or in interactive systems or on the Internet, including journals on the Internet.

- in Clause 5, product strengths will be able to be included in abbreviated advertisements.
- in Clause 6, journal advertisements of up to three consecutive pages will be permissible.
- a new clause is added, to be Clause 7.3, which introduces additional requirements in relation to comparisons.
- in Clause 7, where promotional material refers to data on file, the relevant part of it will have to be provided on request.
- the current Clause 7.10, which precludes the use of other companies' brand names, will be deleted.
- the Medicines Control Agency is added to the list of bodies in Clause 9.4 which cannot normally be referred to in promotional material.
- Clause 12.3, which requires mailing lists of health professionals to be kept up-to-date, will also apply to mailing lists of administrative staff.
- meetings which involve travel outside the UK will have to be certified in advance in a manner similar to that provided for by Clause 14.1.
- added to the supplementary information to Clause 15.3 will be a requirement that reply paid cards which refer to representatives delivering items should explain that there is no obligation to grant the representative an interview when the item is delivered.
- the supplementary information to Clause 16.3 will exhort companies to enter representatives for their examination within their first year of employment.
- certain aspects of Clause 17 will apply to all medicines and not just samples.
- in Clause 17, a sample of a medicine will be able to be provided only to a health professional qualified to prescribe that particular product.
- Clause 17.9 will have further requirements relating to control and accountability of medicines handled by representatives.
- Clause 17.11 will say that medicines may not be sold or supplied to members of the public for promotional purposes.
- Clause 18.1 will cover inducements to recommend a medicine, in addition to inducements to prescribe, supply, administer or buy a medicine.
- the supplementary information to Clause 18.1 relating to the provision of medical and

educational goods and services has been amended to incorporate the guidance in this area issued in November 1999.

- in the supplementary information to Clause 18.1 concerning package deals, the associated benefits will have to be relevant to the medicines involved.
- the limit to the cost of a promotional aid in the supplementary information to Clause 18.2 will be increased from £5 excluding VAT to £6 excluding VAT.
- the supplementary information to Clause 19.1 relating to spouses and other such persons coming to meetings has been clarified.
- in Clause 20, it will be possible to provide European public assessment reports (EPARs) to members of the public on request and the supplementary information will refer to the acceptability of appropriate disease awareness and public health campaigns.
- a completely new clause, to be Clause 21, will deal with the application of the Code to the Internet.

Changes to the Constitution and Procedure

The following are the main changes for the 2001 edition:

- added to the Code of Practice Appeal Board will be a member representative of the interests of patients.
- the Director, Secretary and Deputy Secretary of the Authority will be able to be present at a meeting of the Appeal Board during the consideration of an appeal or a report from the Code of Practice Panel only at the invitation of the Chairman and with the agreement of the parties involved.
- both the complainant and the respondent will be able to be present or represented when the Appeal Board considers an appeal – at present only the respondent company can be represented.
- where a respondent company appeals certain of the Panel's rulings of breaches of the Code but accepts others, it will have to give at that time the requisite undertaking and assurance in acceptance of those rulings not appealed – at present a company can defer doing so until the appeal on the other matters has been completed.
- where a respondent company appeals, the complainant will have an opportunity to comment on the reasons given for the appeal.

CODE OF PRACTICE TRAINING

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

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

Forthcoming Code of Practice seminar dates on which places remain available are:

Monday, 2 July

Tuesday, 31 July

Friday, 14 September

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

For further information regarding any of the above, please contact Jean Rollingson for details (020 7930 9677 extn 1443).

How to contact the Authority

Our address is:

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

Telephone: 020 7930 9677
Facsimile: 020 7930 4554

Copies of the Code of Practice for the Pharmaceutical Industry and of this Review can be obtained from Lisa Matthews (020 7930 9677 extn 1473).

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

Heather Simmonds: 020 7747 1438
Etta Logan: 020 7747 1405
Jane Landles: 020 7747 1415

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

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

ANONYMOUS COMPLAINANT v PHARMAX

Promotion of Syscor MR

An anonymous complainant stated that he and his partners had received a plea from a representative to accept £10 as an 'administration fee' for each patient switched from amlodipine to Pharmax's product Syscor MR (nisoldipine). The representative was apparently under threat of losing their job if they failed to 'sign up' sufficient GPs each week. The complainant provided a copy of an internal memorandum, sent to Pharmax's salesforce, which detailed various representatives' successes in getting doctors to agree to the switch. The complainant alleged that the memorandum implied that representatives were either selecting, or assisting in the selection of, suitable patients for switching in return for payment. The complainant alleged that such a method of promotion was irresponsible.

The Panel was concerned that the memorandum referred to letters being produced and posted to patients and mentioned that a representative was going to 'sit with a doctor to help him select the 20 most appropriate patients!'. A checklist was provided as part of the representatives' briefing material. The first point on the checklist was that the GP had agreed to switch patients from amlodipine to Syscor MR. The checklist reminded representatives that they could pay up to £1 per patient recall letter to cover administration costs. It also mentioned that the practice might need the representatives to come in and help do the computer search with practice staff.

The Panel noted that the principle of changing patients to Syscor MR from other medication was not necessarily unacceptable but the arrangements had to comply with the Code.

The Panel was concerned that the offer of payment to cover the administration costs of recalling patients could be seen as an inducement to prescribe Syscor MR. In addition, the Panel considered that it was not appropriate to encourage representatives to help with a computer search. Neither the memorandum nor the checklist mentioned patient confidentiality. The memorandum implied that representatives did not have to consider this issue and that representatives would assist doctors to identify patients personally as opposed to by type. The Panel considered that the arrangements were unacceptable and that the company had failed to maintain a high standard of ethical conduct and breaches of the Code were ruled. The arrangements were such as to bring discredit upon, and reduce confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled. Pharmax appealed the Panel's rulings.

The Appeal Board noted Pharmax's submission that, although the wording of the memorandum was inappropriate, no representative would have had access to, or seen, patient details on practice computers; they would only have given guidance to practice staff as to how to identify suitable patients for switching. The representatives were aware of the requirements of the Code and understood the issue of patient confidentiality.

The Appeal Board was concerned that the memorandum and the checklist advocated a course of action that would lead to a breach of the Code. There was no mention in either

document of patient confidentiality or clear guidance that representatives must not have direct access to patient records. The memorandum, which had been sent to motivate the sales force, reported how some representatives had assisted doctors or other practice staff to identify patients to switch to Syscor MR. In the Appeal Board's view representatives would assume such actions were acceptable and aspire to do the same. The checklist stated that representatives could pay up to £1 per letter to cover administration costs. The Appeal Board considered that this could be seen as an inducement; it was payment being offered in association with the prescribing of Syscor MR. This was unacceptable.

The Appeal Board upheld the Panel's rulings of breaches of the Code. The Appeal Board considered that the arrangements were such as to bring discredit upon, and reduce confidence in, the pharmaceutical industry. The Panel's ruling of a breach of Clause 2 was upheld.

A complaint sent anonymously by a general practice enclosed a copy of an internal memorandum entitled 'More new business for Syscor!' which Pharmax Limited had sent to its salesforce. The memorandum detailed various representatives' successes in getting doctors to agree to switch patients from amlodipine to Syscor MR (nisoldipine).

It was established practice that anonymous complaints were to be accepted and considered in the usual way.

COMPLAINT

The complainants stated that they had recently received a plea from an obviously distraught medical representative – apparently under constant threat of losing their job when they failed to 'sign up' sufficient GPs each week – to accept ten pounds as an 'administration fee' for each and every patient switched from amlodipine to nisoldipine (Syscor MR).

This was a regrettable, worrying and potentially harmful practice pursued by this company and the complainants requested the Authority's early intervention to curtail it immediately.

The document provided was an internal memorandum which referred to activity by representatives working in two particular geographical areas – the implication was that representatives were either selecting or assisting in the selection of 'suitable patients for switching' in return for payment!

The memorandum was naively offered as an example of just how other practices were participating in this marketing ploy.

The complainants had chosen to retain anonymity out of respect for the local representative who was known and previously respected by the practice. It was the management of the company concerned and not the individual employee who should be asked to account for such irresponsible activity! A copy of the letter of complaint and its enclosure was being forwarded to the medical director of the company. It was hard to believe that the memorandum would have been approved by a member of the medical profession!

RESPONSE

Pharmax stated that firstly it had some concern that the anonymous complaint that the Authority had received was actually from a member of the medical profession. The reasons for its suspicions were that in the accompanying memorandum no mention was made of the geographical locations of either the medical representatives or the doctors. However, the complainant had rightly identified where the representatives were working.

Pharmax's second comment concerned the date of the memorandum, which was issued on Friday, 20 October. The earliest that this could have been received by any of Pharmax's representatives would have been either the Saturday morning or, more likely, Monday, 23 October. It was somewhat surprising therefore that the Authority should have received a complaint so soon after the letter was published.

As would be seen from the memorandum, it was designed to be motivational and in no way had any threat either implied or actual. All the contents were purely congratulating members of the fieldforce who were beginning to establish sales for Syscor MR.

With regard to the issue concerning a 'Syscor MR Switch Programme', Pharmax could categorically confirm that it did not have a structured programme in place. As a small company it had to very much restrict its expenditure and the annual budget for each GP representative, which could be spent on practice meetings and the like, was £2000 per representative. All expenditure from this budget had to be accompanied by a receipt. The budget was primarily designed to be used for in-surgery meetings for which food was provided (a copy of the supermarket till receipt was required to confirm expenditure) or postgraduate meetings where the postgraduate department provided food and, again, a printed receipt from the postgraduate department or the catering company was required to accompany any expenditure. The £2000 covered meetings in hospitals and amongst GPs and included Suscard, Predfoam, Pharmax's community products Sudocrem and Infacol, as well as Syscor MR.

Apart from there being no mechanism whereby an unreceipted expenditure could be claimed, the sheer financial logistics mitigated against any scheme such as proposed in the letter, ie £10 per patient. A practice offering up say 70 patients would require funding of £700. This would use up virtually half of the GP representative's annual budget.

To further confirm that such practices had not taken place unbeknown to the company, Pharmax's accounts department had carried out a full audit of

expenditure from the beginning of the company's fiscal year (1 April 2000) and it had confirmed that no such expenditure had occurred.

With regard to Pharmax's ethos, if the Authority checked its records it would be found that Pharmax adhered strictly to the Code and in no circumstances would it consider any activities that would damage either the company's reputation or that of the industry as a whole.

In response to a request for further information Pharmax stated that the promotional platform for Syscor MR was focused on cost but the company did not operate a structured switch programme. Representatives had been briefed to outline the benefits of Syscor MR both clinically and financially to GPs (in terms of cost savings to the prescribing budget). No financial inducement of any kind was offered to the practice or individual GPs to switch patients other than the cost savings that they themselves would make once they were convinced of the clinical benefits of Syscor MR.

With regard to the complainant's allegation that a £10 administration fee to switch patients from amlodipine to Syscor MR had been offered, there was no mechanism within the company whereby an unreceipted expenditure could be claimed by an individual representative. The relatively small size of the A/V budget issued to each representative (£2000 per half year) would also make such an offer unsupportable since a practice switching 50 patients at a cost of £10 per patient would use up 25% of a representative's budget. As previously stated the accounts department carried out a full audit of expenditure by representatives during the fiscal year and had confirmed that no such expenditure had occurred.

With regard to the memorandum dated 20 October which referred to letters being posted out to patients, the company confirmed that it was not involved in any way in the actual preparation or posting out of letters to patients.

In response to a request for a copy of the representatives' briefing material the company provided a copy of a checklist which was produced as an aide memoire for representatives to help them work with practices to ensure a smooth transition to Syscor MR in the appropriate patients.

Point 1 clearly stated that 'GP has agreed to switch patients from amlodipine to Syscor MR'. This starting point was only achieved if a representative had convinced the GP that both clinically and in terms of cost benefits Syscor MR was an appropriate product to use. Further point 6c offered guidance on what a representative could pay to cover administration costs. It clearly stated 'for example you could pay up to £1.00 per letter for administration costs'. Pharmax submitted that this was not unreasonable when the cost of first class postage, paper, printer ink, envelopes and administration time were considered.

A copy of the Syscor MR promotional material supplied to representatives was provided.

With regard to the role of representatives when practices had agreed to change patients' medication,

Pharmax confirmed that representatives were trained to a high standard to comply with Clause 15.1 and as such could assist GPs in selecting the most suitable patients (by type) for Syscor MR. As a service to the GP, they could offer assistance to the practice to enable it to identify patients by advising them about the correct selection criteria. This was purely an offer of assistance, which the practice might accept or decline, and certainly no payment was offered for doing this. Thus if any representatives assisted in selecting patients it was at this level and with full agreement of the practice.

Finally, with regard to the reference in the memorandum dated 20 October to sending out weekly updates, Pharmax advised that due to a lack of further responses the author had not been able to send out any further memoranda on successful switches.

PANEL RULING

The Panel was concerned about the arrangements set out in the memorandum dated 20 October which had been sent to the ethical salesforce. The memorandum frequently referred to 'switching' and the 'switch programme' and discussed the successes of several individual representatives in achieving product switches from amlodipine and felodipine to Syscor MR. It referred to letters being produced and posted to patients and mentioned that a representative was going to 'sit with the doctor to help him select the 20 most appropriate patients!'. Reference was also made to a representative returning to a practice 'each Thursday afternoon to seek out an additional 20 patients'. The checklist was part of the representatives' briefing material and headed 'Checklist for switches'. The first point on the checklist was that the GP had agreed to switch patients from amlodipine to Syscor MR. The checklist reminded representatives that they could offer to pay up to £1 per patient recall letter to cover the administration costs. It also mentioned that the practice might need the representative to come in and help do the computer search with practice staff.

The Panel noted that the principle of changing patients to Syscor MR from other medication was not necessarily unacceptable. The Panel considered that the arrangements nevertheless had to comply with the Code.

The Panel noted that neither the memorandum nor the checklist referred to the £10 administration fee mentioned by the complainant. The Panel was concerned about the offer of a payment of up to £1 per letter to cover administration costs of recalling patients to the surgery to change their therapy. In effect it could be seen as an inducement to prescribe Syscor MR. This was unacceptable. The Panel ruled a breach of Clause 18.1 of the Code.

The Panel considered that the arrangements regarding the representatives were unacceptable. It was not appropriate to encourage the representatives to help with a computer search. No mention was made of patient confidentiality issues in either the memorandum or the 'Checklist for switches'. The memorandum implied that the representatives did not

have to consider this issue. In the Panel's view it also implied that representatives would assist doctors to identify patients personally, as opposed to by type as submitted by Pharmax. The Panel noted that guidance on the provision of medical and educational goods and services had been issued in the November 1999 edition of the Code of Practice Review. The guidance stated that representatives should not be given access to records that could identify or be linked to particular patients.

The Panel considered that the arrangements were such as to bring discredit upon, and reduce confidence in, the pharmaceutical industry. The Panel ruled a breach of Clause 2 of the Code. The Panel also considered that the company had failed to maintain a high standard of ethical conduct and a breach of Clause 9.1 of the Code was ruled.

APPEAL BY PHARMAX

Pharmax stated that although it accepted the Authority's commitment to dealing with anonymous complaints, in the past such complaints had always been backed up by tangible evidence (usually accepted by the company), demonstrating that a breach of the Code had actually occurred.

Pharmax submitted that there was no evidence that this complaint originated from a medical practitioner, and, indeed, the Authority had on several occasions confirmed that it received, with no additional evidence, the same anonymous letter that was sent to Pharmax. Arguably the letter was a deliberate attempt to mislead the Authority. There were certain phrases eg 'document would have been approved' which suggested that the author was an individual with inside knowledge of the pharmaceutical industry. Most doctors remained in ignorance of the Code, especially with regard to how it operated within the pharmaceutical industry and the mechanisms of the approval process. Pharmax contended that were the letter to have originated from a GP, a reasonable GP would have identified himself or herself to the Authority and then requested anonymity. Headed paper from a group practice could also have been used without disclosing the identity of the author. There was, therefore, more than reasonable doubt that a medical practitioner actually authored this document of complaint.

Pharmax stated that with regard to the memorandum entitled 'More new business for Syscor', this was a privileged internal communication. It was a letter documenting activities that had occurred. It was not briefing material as it did not discuss the properties of the product nor inform representatives how they should promote the product. It was merely a letter documenting historical events, written with an encouraging upbeat marketing tone.

Pharmax noted that the complainant made comment about 'Code of Practice approval' of the memorandum. The document, as noted above, was not briefing material and was not subject to the Code. It was surprising to Pharmax that the complainant, as a GP, should have considered such a subtle issue, and lent weight to its suspicion that the complaint did not originate from a medical practitioner.

Concerning the complainant's statement that he was offered financial inducement to prescribe Syscor MR, Pharmax vigorously maintained that no financial inducements had been offered and the company therefore denied a breach of Clause 18.1. The only monies mentioned by Pharmax was a suggestion of £1 to contribute to the cost of sending letters to patients requiring change of treatment. Given the current market rate for the production and despatch of a small number of letters, £1 did not even cover costs let alone act as an inducement. As stated earlier, an audit of the company's accounts confirmed that no unauthorised expenditure had occurred (Pharmax noted that in order for a representative to reclaim any expenditure, a fully receipted invoice had to be submitted). Pharmax also categorically refuted the suggestion made by the complainant that medical representatives were threatened with loss of employment as a consequence of failing to sell Syscor MR.

Pharmax stated that with regard to comment about the alleged 'switch programme', there had never been a switch programme organised or initiated by the company. It was common business practice throughout the economy to encourage competition, and one aspect of this was that whenever an alternative similar product that was cheaper could be substituted, it was common sense to do so. Similarly the NHS was concerned about the cheapest therapy to do the job. Thus all that was taking place was a proposition to GPs to identify patients who could change treatment safely and save the practice money. The inducement was that the practice could save up to 21% by changing from amlodipine 5mg to Syscor MR 10mg.

The regional manager and all of the representatives from the two geographical areas mentioned in the memorandum had been interviewed. They had individually confirmed that at no time did they see or ask to see any patient records. All that was suggested was that they assisted the practice in identifying instances of amlodipine use where a change might be made. There was no need or suggestion that confidential patients' notes would be seen – this was of no interest and there had been no instance where staff were asked to breach confidentiality. The only useful search was by type ie hypertension and using amlodipine.

In conclusion Pharmax submitted that this complaint raised several issues.

Whilst the Authority had considered anonymous complaints in the past, there had usually been evidence to support the claim. In this case, there was no evidence that any of the events took place, and there was no evidence that the letter originated from a medical practitioner. Given that the author was so conversant with promotional matters, it was worrying that Pharmax might have been the victim of a malicious attempt to disrupt its business. It was inappropriate for the company to speculate but it could not exclude the possibility of this being the activity of a competitor company or a disgruntled ex-employee.

Pharmax stated that the fact that the memorandum was enclosed with the complaint must also raise some

questions. The memorandum was produced on 20 October (a Friday), received at the earliest on Monday (23 October) and the letter of complaint was sent on Friday (27 October). Very fast work for a busy general practitioner!

Pharmax stated that the Appeal Board should in addition consider the fact that if there was an adverse finding published from an anonymous allegation without tangible evidence, it could open the way for any number of anti-industry groups to cripple the commercial process. Pharmax was being asked to provide evidence of innocence, when in fact, the claimant should be asked to provide evidence of misdemeanour.

Pharmax and its representatives had never sought nor been instructed to sell its products by financial inducement. The company had thoroughly audited its records and systems to confirm that such a flow of monies could never have happened.

Pharmax denied that the events outlined in the complaint, alleging financial inducements for prescribing Syscor MR and threats to the livelihood of sales representatives, ever took place, and there was no evidence whatsoever to support these cruel and malicious allegations.

Given the lack of tangible and supportable evidence to substantiate the complaint and the strong possibility that this letter might have been the work of somebody who was not a medical practitioner, Pharmax proposed that the complaints against it be dropped.

APPEAL BOARD RULING

The Appeal Board noted the submission from Pharmax and the points made by Pharmax at the appeal hearing. The company representatives had acknowledged that the choice of words in the internal memorandum dated 20 October was inappropriate but had given assurances that no representative would have seen the patient details on practice computers or would have had access to patient details. The medical representatives would only have given guidance to practice staff as to how to identify those patients who might be suitable for switching to Syscor MR. Each representative had been questioned. The representatives were well trained on the Code and representatives were fully aware of the its requirements and of the company's strict adherence to it. The company representatives had been confident that the medical representatives understood the issue of patient confidentiality.

The Appeal Board noted Pharmax's concerns about the anonymous complaint. Nevertheless the complaint had to be dealt with. The allegation referred to the provision of £10 as an administration fee for every patient switched from amlodipine to Syscor MR. A copy of the internal memorandum had been provided by the complainant. As with all cases involving representative activities Pharmax had been asked for the relevant briefing material which consisted of both the training material used to instruct representatives about a medicine and how that medicine should be promoted (supplementary

information to Clause 15.9 of the Code). In response to this Pharmax had provided the document headed 'Checklist for switches'. This had not been certified in accordance with Clause 14 of the Code.

The Appeal Board noted the submission that the sum available, £1 per patient, was to cover administration costs. Pharmax submitted that it was only offered once the practice had agreed to a switch and had indicated that it would have difficulty in funding the letters recalling patients to the surgery.

The Appeal Board was concerned that the documents before it, the internal memorandum and the checklist, amounted to inappropriate instructions to representatives in that they advocated a course of action that would lead to a breach of the Code. The internal memorandum had been sent to motivate the sales force and referred to the switch programme, stating that a representative had 'sat with the doctor to help him select the 20 most appropriate patients'. Another representative was to return to the practice 'each Thursday afternoon to seek out an additional 20 patients'. One representative was offered a free hand to undertake the switch programme via the practice nurse. The same representative had been provided with access to help organise successful switch programmes. In the Appeal Board's view representatives would assume that such actions were acceptable and aspire to do the same. The checklist stated that representatives could offer to pay up to £1 per letter to cover administration costs. It also referred to representatives helping to do the computer search with the practice staff. The documents would be seen as advocating acceptable mechanisms for representatives to use when promoting Syscor MR and this was not so.

The Appeal Board considered that the offer of £1 per letter to cover administration costs of recalling

patients to change their medication, which was clearly company policy as shown in the checklist, could be seen as an offer of an inducement to general practitioners to prescribe Syscor MR. It was payment being offered in association with the prescribing of Syscor MR. This was unacceptable. The Pharmax representatives had stated that there had been very little money paid out and that almost none of the representatives had been reimbursed. The Appeal Board upheld the Panel's ruling of a breach of Clause 18.1 of the Code. The appeal on this point was unsuccessful.

The Appeal Board considered that with regard to representatives and their access to practice computers, the memorandum and checklist appeared to advocate action which would be unacceptable under the Code; both documents implied that it was acceptable for representatives to assist in the identification of patients. There was no mention of patient confidentiality or clear guidance that the representatives must not have direct access to patient records.

The Appeal Board considered that the arrangements were such as to bring discredit upon, and reduce confidence in, the pharmaceutical industry. The Appeal Board upheld the Panel's ruling of a breach of Clause 2 of the Code. The Appeal Board also considered that the company had failed to maintain a high standard of ethical conduct and upheld the Panel's ruling of a breach of Clause 9.1 of the Code. The appeals on these points were unsuccessful.

Complaint received	31 October 2000
Case completed	28 February 2001

ASTRAZENECA v ALLEN & HANBURYS

Accuhaler 'Dear Doctor' letter

AstraZeneca complained about a 'Dear Doctor' letter entitled 'A is for Accurate' which had been sent by Allen & Hanburys. The subheading read 'Are your asthma patients getting the right dose of medication all the time?' and the letter concerned the choice between the Ventolin Accuhaler (Allen & Hanburys) and the terbutaline 'turbo-inhaler' (AstraZeneca's Turbohaler) with reference to inspiratory flow rates. The letter stated that the Accuhaler consistently delivered over 89% of the medicine even at low inspiratory flow rates. This was immediately followed by a statement that the turbo-inhaler demonstrated variability in drug delivery of between 54% and 99% over a range of inspiratory flow rates. The postscript to the letter referred to a competition whereby 100 winners would each receive an In-Check Dial which would provide a means of assessing a patient's ability to use certain inhaler devices. The letter had also been the subject of Case AUTH/1078/9/00.

In relation to the claim 'Are your asthma patients getting the right dose of medication all the time?', AstraZeneca alleged that the tone of the claim was misleading and inappropriate in that it implied that any device which was not the Accuhaler was potentially harmful and not delivering the correct dose. The positioning of the Accuhaler image immediately adjacent to the statement reinforced the misleading tone. In the Panel's view, the claim at issue did more than merely raise the general subject of dose consistency both through the life of the device and at various flow rates as stated by Glaxo Wellcome. The Panel noted the prominence and juxtaposition of the claim at issue, the Accuhaler image and the main heading 'A is for accurate'. The Panel also noted that the letter referred to dose consistency with reference to the Accuhaler. A graph included in the letter favourably compared the dose consistency of the Accuhaler over a range of inspiratory flow rates with that of a terbutaline turbo-inhaler. The Panel considered that the layout and content of the letter were such that the claim inferred that other devices were not delivering the correct dose and was misleading in this regard. A breach of the Code was ruled.

The first sentence of the letter read 'Once you have made the decision to prescribe a dry powder inhaler – let's make the choice easy' and was followed by two bullet points; the first discussed the drug delivery of Accuhaler at low inspiratory flow rates and the second referred to the turbo-inhaler's variability in drug delivery over a range of inspiratory flow rates. AstraZeneca stated that the choice of inhaler device for an individual patient was a clinical process which involved a detailed interaction with the healthcare professional. The final choice was made after due consideration of many individual patient factors and appropriate training with the inhaler device. The statement implied that inspiratory flow rate was the only factor that needed to be considered. This was clearly not the case and it was therefore over simplistic and misleading. The Panel noted that in an earlier case, AUTH/1078/9/00, concerning the same letter, which had not been decided when the current complaint was received, the Panel had considered that 'making the choice easy' made it appear that inspiratory flow rate was the only parameter that

needed to be considered when choosing a dry powder inhaler. The Panel had considered that the letter, by implying clinical benefit from the results of an *in vitro* study of only one parameter that was important in determining the respirable dose, was misleading. A breach of the Code had been ruled and this had been accepted by Glaxo Wellcome. The Panel considered that its ruling in Case AUTH/1078/9/00 also applied here and a breach of the Code was ruled.

In relation to a reference to Malton *et al* (1996), AstraZeneca stated that the fact that this was *in vitro* data was not mentioned in the letter itself. This implied that the findings could be extrapolated into clinical effectiveness which could only be reasonably implied in the light of a suitable clinical study. Such a study would need to compare both the Turbohaler and the Accuhaler at different flow rates and show that clinical effectiveness was significantly different. In the absence of such a study, it was misrepresentation of data and misleading to use this reference to support this and any related claims. The Panel observed that in Case AUTH/1078/9/00 it had noted that the study by Malton *et al* was an *in vitro* investigation but this point had not been stated. The Panel had ruled a breach of the Code. This ruling had been accepted by Glaxo Wellcome. The Panel considered that the ruling also applied in this case and a breach of the Code was ruled.

The claim 'This means that the patient, and you, can be confident that they are receiving a consistent dose of medication when they use their Accuhaler' was preceded by the statement 'The Accuhaler delivers consistent doses even at low inspiratory flow rates (30L/min) through the life of the device. The dose consistency is demonstrated by the graph'. The graph depicted the results of Malton *et al*. The Panel considered that its rulings above were relevant here. The clinical claim was immediately preceded by statements which discussed the *in vitro* study by Malton *et al*. A breach of the Code was ruled.

The claim 'This may be important in children and patients whose asthma is deteriorating, who may have low inspiratory flow rates' immediately followed the claim considered above. AstraZeneca alleged that without clinical studies that clearly demonstrated that a lower inspiratory flow rate through a Turbohaler was detrimental in terms of clinical benefit derived from the inhaler device, this claim was misleading and poorly representative of the balance of clinical data. Pedersen *et al* (1990) showed that the beneficial clinical effects of the Turbohaler were retained down to inspiratory flow rates of 30L/min (the lowest flow rate quoted on the graph in the letter). Brown *et al* (1995) demonstrated in a study of 99 patients attending with acute

exacerbations of asthma, that 98% generated an inspiratory flow rate of 30L/min. Engel *et al* (1992) found similar bronchodilation at inspiratory flow rates between 34 to 88L/min. In Case AUTH/1078/9/00, the Panel had considered that the 'Dear Doctor' letter cast doubt upon the efficacy of the Bricanyl Turbohaler in children and those presenting with acute asthma. The Panel had considered that the letter was misleading in this respect and a breach of the Code was ruled. The ruling had been accepted by Glaxo Wellcome. The Panel considered the ruling in Case AUTH/1078/9/00 applied here and a breach of the Code was ruled. Upon appeal by GlaxoSmithKline (which Glaxo Wellcome had by then become), the Appeal Board noted that Section 6.6 of the summaries of product characteristics (SPCs) for the Oxis Turbohalers (6mcg and 12mcg) advised the prescriber that it was important to instruct the patient to breathe in forcefully and deeply through the mouthpiece to ensure that an optimal dose was obtained. The Appeal Board further noted GlaxoSmithKline's submission that AstraZeneca had amended the instructions in the Turbohaler PIL from 'Breathe in deeply' to 'Breathe in deeply and as hard as you can'. The claim was that consistency of dose may be (emphasis added) important in children and patients whose asthma was deteriorating and who may have low inspiratory flow rates. The Appeal Board did not consider that the claim was unreasonable and therefore ruled no breach of the Code.

The claim 'Appreciating the importance of accurate assessment of inspiratory flow rate in allowing you to choose the most appropriate inhaler for your patients' appeared at the start of the postscript to the letter. AstraZeneca referred to the points made above which highlighted the process for choosing the right inhaler device for the patient. Assessment of inspiratory flow rate was not established within current clinical practice as the overwhelming feature in the choice of inhaler device. Indeed personal training and assessment with the device was the feature consistently accepted as good clinical practice. However, this had been neglected in this letter. Persson *et al* (1997) demonstrated that appropriate inhaler training could optimise the use of the Turbohaler allowing patients to achieve higher inspiratory flow rates, even in severe asthma. The Panel considered that its ruling made in Case AUTH/1078/9/00 and detailed above was relevant with regard to the number of factors which could affect the respirable dose. Inspiratory flow rate was one of a number of important issues in determining clinical outcome and choice of inhaler. The Panel considered that the claim at issue was sufficiently broad; it did not state or imply that inspiratory flow rate was the only important factor when choosing an inhaler. No breach of the Code was ruled.

In relation to the offer of free In-Check Dial devices, AstraZeneca stated that it firmly believed that the current design of the device misrepresented the ease of use and the clinical benefits derived from the Turbohaler (in relation to other inhaler devices assessed by the In-Check Dial). The In-Check Dial set inappropriate levels of inspiratory flow rate for the Turbohaler. It specifically implied that the

Turbohaler could not be used with inspiratory flow rates of less than 60L/min. This contradicted the balance of clinical evidence. As such, the free offer was misleading and an inducement that unfairly encouraged the recipient to prescribe other devices ahead of the Turbohaler. The Panel noted that the In-Check Dial was a device which comprised a low range inspiratory flow meter (15 to 120L/min) that had a selectable resistance calibrated to enable measurement of airflow as if the patient was using the following inhalers; Turbohaler, Accuhaler/Diskus, Autohaler and the Easi-Breathe/Surehaler. The Panel noted that the Code applied to the promotion of medicines and not to the promotion of devices *per se*. The In-Check Dial was provided as a competition prize. The competition formed part of a promotional mailing for the Ventolin Accuhaler. The Panel considered that the provision of the In-Check Dial by Glaxo Wellcome in such circumstances came within the scope of the Code. A table which appeared on a card accompanying the In-Check Dial, headed 'Optimum Inspiratory Flow', showed the inspiratory flow rates for the Accuhaler at 30-90 L/min, Turbohaler 60-90L/min, Autohaler 30-60L/min and Easi-Breathe at 20-60L/min. Similar information appeared on the In-Check Dial itself without the reference to 'Optimum Inspiratory Flow' and using symbols for the different types of inhalers. The Panel noted Glaxo Wellcome's submission that nowhere was it implied that the Turbohaler could not be used with inspiratory flow rates of less than 60L/min. The Panel considered that a ruling above was particularly relevant here with regard to the effectiveness of the turbohaler at low inspiratory flow rates in children and those presenting with acute asthma. The Panel considered that given its rulings above on the content of the 'Dear Doctor' letter, the table of inspiratory flow rates on the In-Check Dial created the impression, in conjunction with the 'Dear Doctor' letter, that the Turbohaler could not be used at all with inspiratory flow rates of less than 60L/min. In this regard the Panel considered that the use of the In-Check Dial as a prize in a promotional competition by Glaxo Wellcome was misleading and a breach of the Code was ruled. Upon appeal by GlaxoSmithKline, the Appeal Board considered that the information on the In-Check Dial itself without further explanation implied that only patients with an inspiratory flow rate of between 60 and 90L/min could use the Turbohaler and that was not so. The range for the maximum effect was 60-90L/min. The Appeal Board considered that the inadequate labelling on the device itself was such that its use for a promotional purpose was misleading. The Appeal Board upheld the Panel's ruling of a breach of the Code.

AstraZeneca UK Limited complained about a 'Dear Doctor' letter (ref HM5537-Alp/May 2000) entitled 'A is for Accurate' which had been issued by Allen & Hanburys Limited. The subheading read 'Are your asthma patients getting the right dose of medication all the time?' and the letter concerned the choice between the Ventolin Accuhaler (Allen & Hanburys) and the terbutaline 'turbo-inhaler' (AstraZeneca's Turbohaler) with reference to inspiratory flow rates. The letter stated that the Accuhaler, even at low

inspiratory flow rates, consistently delivered over 89% of the medicine. This was immediately followed by a statement that the turbo-inhaler demonstrated variability in drug delivery of between 54% and 99% over a range of inspiratory flow rates.

The postscript to the letter referred to a competition whereby 100 winners would each receive an In-Check Dial which would provide a means of assessing a patient's ability to use certain inhaler devices.

The Authority advised Glaxo Wellcome that some of the issues in the present case were closely similar to a recent case, Case AUTH/1078/9/00, which concerned the same 'Dear Doctor' letter. At the time of receipt of this complaint the previous complaint had not been completed. At the time of consideration of this case the previous case had been completed with no appeals from either party. The letter was last used in June 2000.

1 Claim 'Are your asthma patients getting the right dose of medication all the time?'

COMPLAINT

AstraZeneca stated that it fully supported the view that the appropriate delivery of inhaled medication was of paramount importance in asthma management. Indeed, effective drug delivery through the inhaled route was the cornerstone of good clinical practice for asthma in the UK. However, the tone of the statement was misleading and inappropriate in that it implied that any device which was not the Accuhaler was potentially harmful and not delivering the correct dose. The positioning of the Accuhaler image immediately adjacent to the statement reinforced the misleading tone.

RESPONSE

Glaxo Wellcome stated that there was no implication within this statement that 'any device which was not the Accuhaler was potentially harmful and not delivering the correct dose'. Glaxo Wellcome was however raising the general subject of dose consistency both through the life of the device and at various flow rates. In both of these aspects the Accuhaler had been shown to have good qualities of dose consistency.

PANEL RULING

In the Panel's view, the claim at issue did more than merely raise the general subject of dose consistency both through the life of the device and at various flow rates as stated by Glaxo Wellcome. The Panel noted the prominence and juxtaposition of the claim at issue, the Accuhaler image and the main heading 'A is for accurate'. The Panel also noted that the letter referred to dose consistency with reference to the Accuhaler. A graph included in the letter favourably compared the dose consistency of the Accuhaler over a range of inspiratory flow rates with that of a terbutaline turbo-inhaler. The Panel considered that the layout and content of the letter were such that the claim inferred that other devices were not delivering the correct dose and was misleading in this regard. A breach of Clause 7.2 was ruled.

2 Claim 'let's make the choice easy'

The first sentence of the letter read 'Once you have made the decision to prescribe a dry powder inhaler – let's make the choice easy' and was followed by two bullet points; the first discussed the drug delivery of Accuhaler at low inspiratory flow rates and the second referred to the turbo-inhaler's variability in drug delivery over a range of inspiratory flow rates.

COMPLAINT

AstraZeneca stated that the choice of inhaler device for an individual patient was a clinical process which involved a detailed interaction with the healthcare professional. The final choice was made after due consideration of many individual patient factors and appropriate training with the inhaler device. The statement implied that inspiratory flow rate was the only factor that needed to be considered. This was clearly not the case and it was therefore over simplistic and misleading.

RESPONSE

Glaxo Wellcome refuted this complaint, in that nowhere in the mailing did it suggest that inhaled drug delivery and efficacy were simply outcomes of inspiratory flow. It should be taken into account that the phrase 'let's make the choice easy', came at the end of a sentence in which it was implied that a decision making process had already been involved in reaching the decision to prescribe a dry powder inhaler.

However it had been accepted and understood for many years that the effort a patient put into inspiring through a dry powder inhaler device might affect the dose of drug that was delivered, and that this in turn might affect clinical outcome.

Dry powder inhalers used energy, generated within the device during inhalation, to promote dispersion and de-aggregation of the powder, thus producing particles of respirable size (between 2 and 5 microns). The level of energy generated inside each dry powder inhaler, from a set inhalation rate, was dependent on the resistance in the device. As inspiratory effort was proportional to inspiratory flow rate multiplied by the device resistance, it was easier to generate a given inspiratory flow through a device with low internal resistance than through one with high internal resistance. Richards and Saunders (1993) showed that to achieve a flow of 60 litres/minute through the Turbohaler, three times the inspiratory effort was needed compared with the Diskhaler.

Everard *et al* (1996) evaluating the Turbohaler stated 'inspiratory flow and the flow profile should be considered when assessing any dry powder inhaler'. An Astra study, Olsson and Asking (1994), stated that 'The flow rate attained by a patient depends on the effort expended and on the air flow resistance of the device. A comparison between powder inhalers should therefore take their air flow resistances into account'.

As inspiratory effort was proportional to inspiratory flow rate multiplied by the device resistance, it was easier to generate a given inspiratory flow through a

device with low internal resistance than through one with high internal resistance. Indeed, Andersen (1993) found that the majority of patients preferred to inhale from a device with a lower internal resistance than from a device with a high resistance.

It was thus generally accepted that internal resistance and inspiratory flow rate were important aspects of dry powder inhalers and should be considered in device selection.

PANEL RULING

The Panel considered that part of its ruling at Case AUTH/1078/9/00 was relevant here.

Relevant part of ruling in Case AUTH/1078/9/00: The Panel noted that the 'Dear Doctor' letter began by stating 'Once you have made the decision to prescribe a dry powder inhaler – let's make the choice easy'. The letter then detailed the results of a study by Malton *et al* which was an *in vitro* comparison of the drug delivery characteristics of Allen & Hanburys' Ventolin Accuhaler and AstraZeneca's Bricanyl Turbohaler. The study demonstrated that at inspiratory flow rates of 30, 60 and 90 litres/minute the Turbohaler delivered between 54% and 99% of the stated dose whilst over the same range of flow rates the Accuhaler consistently delivered over 89%. The authors concluded that the dose consistency seen with the Accuhaler was clinically relevant and the reduction in dose delivery from the Turbohaler seen at 30 litres/minute might have clinical implications.

The results of the Malton study were shown in a bar chart in the letter. The presentation of the results was followed by the statement 'This means that the patient, and you, can be confident that they are receiving a consistent dose of medication when they use their Accuhaler'. In the Panel's view the results from an *in vitro* study were clearly being linked to a clinical benefit. The Panel considered that the letter implied that at inspiratory flow rates of less than 90 litres/minute the Turbohaler would be less efficacious than the Accuhaler. The Panel considered, however, that in the clinical situation the respirable dose was not just dependent upon inspiratory flow rate but also the powder formulation as well as patient training and compliance. The letter made no mention of these other variables nor did it state that inspiratory flow rate was just one of a number of important issues in determining clinical outcome. By 'making the choice easy' it appeared that inspiratory flow rate was the only parameter that needed to be considered when choosing a dry powder inhaler. The Panel considered that the letter, by implying clinical benefit from the results of an *in vitro* study of only one parameter that was important in determining the respirable dose was misleading. A breach of Clause 7.2 was ruled. This ruling had been accepted by Glaxo Wellcome.

Panel ruling in Case AUTH/1096/11/00. The Panel considered that its ruling in Case AUTH/1078/9/00 would also apply to this complaint. The claim at issue implied that inspiratory flow rate was the only factor that needed to be considered and was over simplistic and misleading as alleged. A breach of Clause 7.2 of the Code was ruled.

3 Reference: Malton *et al* (1996)

COMPLAINT

AstraZeneca stated that the fact that this was *in vitro* data was not mentioned in the letter itself. This implied that the findings could be extrapolated into clinical effectiveness. Although Glaxo Wellcome had undertaken to make the nature of this data clear in future, AstraZeneca considered that it was important to raise the issue that clinical effectiveness could only be reasonably implied in the light of a suitable clinical study. Such a study would need to compare both the Turbohaler and the Accuhaler at different flow rates and show that clinical effectiveness was significantly different. In the absence of such a study, it was misrepresentation of data and misleading to use this reference to support this and any related claims.

RESPONSE

Glaxo Wellcome stated that it had been agreed in discussions with AstraZeneca that this reference should have made clear that it was an *in vitro* study. An assurance was given in writing to AstraZeneca in October 2000 that if the reference was to be used in any context in the future, then the *in vitro* nature of the study would be made clear.

However Glaxo Wellcome believed that there was strong clinical support for the relevance of the results from this study.

PANEL RULING

The Panel considered that the comments it made about Malton *et al* in its ruling in Case AUTH/1078/9/00, and detailed in point 2 above, were relevant here. The Panel also noted an additional relevant part of its ruling at Case AUTH/1078/9/00.

Additional relevant part of ruling in Case AUTH/1078/9/00: The Panel noted that it was a principle under the Code that promotional material referred to the clinical situation unless it was clearly stated otherwise. The study by Malton *et al* was an *in vitro* investigation although this point had not been stated in the 'Dear Doctor' letter. The Panel considered that the letter was misleading in this respect and ruled a breach of Clause 7.2 of the Code. This ruling had been accepted by Glaxo Wellcome.

Panel ruling in Case AUTH/1096/11/00: Turning to the present case the Panel considered that its ruling in Case AUTH/1078/9/00 applied here and a breach of Clause 7.2 was ruled.

4 Claim 'This means that the patient, and you, can be confident that they are receiving a consistent dose of medication when they use their Accuhaler'

This claim was preceded by the statement 'The Accuhaler delivers consistent doses even at low inspiratory flow rates (30 L/min) throughout the life of the device. The dose consistency is demonstrated by the graph'. The graph depicted the results of Malton *et al*.

COMPLAINT

AstraZeneca alleged that taken within the context of the letter (and preceding statements), the implication was that the Accuhaler was the only device to deliver a consistent dose, which was misleading.

RESPONSE

Glaxo Wellcome did not consider that it made any claim or assertion that the Accuhaler was the only device to deliver a consistent dose. However the evidence for dose consistency with the Accuhaler did support this statement and it considered that it was entitled to make such a claim.

PANEL RULING

The Panel considered that its rulings at points 1, 2 and 3 above were relevant here. The clinical claim was immediately preceded by statements which discussed the *in vitro* study by Malton *et al.* A breach of Clause 7.2 was ruled.

5 Claim 'This may be important in children and patients whose asthma is deteriorating, who may have low inspiratory flow rates'

This claim immediately followed the claim at issue in point 4.

COMPLAINT

AstraZeneca alleged that without clinical studies that clearly demonstrated a lower inspiratory flow rate through a Turbohaler was detrimental in terms of clinical benefit derived from the inhaler device, this claim was misleading and poorly representative of the balance of clinical data.

AstraZeneca drew attention to studies that supported its emphasis on clinical data on the Turbohaler. Pedersen *et al* (1990) showed that the beneficial clinical effects of the Turbohaler were retained down to inspiratory flow rates of 30L/min (the lowest flow rate quoted on the graph in the letter). Brown *et al* (1995) demonstrated in a study of 99 patients attending with acute exacerbations of asthma, that 98% generated an inspiratory flow rate of 30L/min. Engel *et al* (1992) found similar bronchodilation at inspiratory flow rates between 34 to 88L/min.

RESPONSE

Glaxo Wellcome accepted that there was a statement in the data sheet/summary of product characteristics (SPC) for Bricanyl Turbohaler relating to its effectiveness in adults and children with acute asthma, however, clinical studies had demonstrated that low inspiratory flow might affect response to inhaled therapy. This might mean that a patient with deteriorating asthma might require more doses than expected if delivery was inadequate due to the delivery characteristics of the device under some conditions.

Nielsen *et al* (1998) evaluated the clinical effect of the Accuhaler at low and high flow rates. The authors concluded 'consistent *in vitro* fine particle dosing from

the Diskus [Accuhaler] inhaler translates into consistent clinical effect at low and high flow rates in children'.

Hirsch *et al* (1997) evaluated the effectiveness of bronchodilatation with terbutaline delivered through the Turbohaler in 118 children with asthma. They found significant differences in bronchodilatation, which correlated with inspiratory flow. The authors concluded that 'When using the Turbohaler for bronchodilatation, the effectiveness of terbutaline depends upon the degree of inspiratory capacity. This can lead to impaired bronchodilatory effect in subgroups of obstructive young asthmatics with low inspiratory flow. In contrast when using a pMDI, inspiratory capacity does not seem to influence the effectiveness of terbutaline'.

Borgström *et al* (1996), a study sponsored by Astra, assessed the lung deposition and bronchodilating effect of terbutaline through the Turbohaler and found that reduced deposition was associated with reduced bronchodilating effect.

Glaxo Wellcome was aware that AstraZeneca had referenced three studies.

The first study (Pedersen *et al*) evaluated the influence of inspiratory flow resistance on the effect of a Turbohaler. In the complaint AstraZeneca incorrectly commented on the study findings when it stated that 'the beneficial clinical effects of the Turbohaler were retained down to inspiratory flow rates of 30 L/min.' Pedersen *et al* actually reported that 26% of children under six years and 60% of children with acute wheeze could not generate an inspiratory flow rate of 30 L/min.

Importantly, the authors of this paper stated that 'Young children may gain less benefit from the treatment [Turbohaler] because they cannot generate sufficiently high inspiratory flow rates, especially during episodes of acute bronchoconstriction. This may also be true for a few older children during episodes of acute wheeze'.

The second study referenced by AstraZeneca was also incorrectly commented upon. AstraZeneca stated 'that Brown *et al* demonstrated in a study of 99 patients attending with acute asthma, that 98% generated an inspiratory flow rate of 30 litres/minute'. The authors of this study, which was sponsored by Astra, in fact reported that 9% might not be able to achieve an inspiratory flow of 40 litres/minute. If the data were analysed it could be seen that 50% of adults in this study were not able to achieve an inspiratory flow of 60 litres/minute through the Turbohaler. This study was performed using an empty Turbohaler and no terbutaline was inhaled to assess the actual clinical effect.

An Astra paediatric study (Bisgaard *et al* 1994) found an age dependent increase in ability to use the Turbohaler with considerable scatter across age groups, and concluded that the dose delivered could not be predicted in young children. It had also been shown that the maximal inspiratory flow rates generated by young asthmatic children might be insufficient for effective operation of high resistance dry powder inhalers (Bisgaard *et al* 1998).

De Boeck *et al* (1999) evaluated the ability of children with asthma to use a Turbohaler. They found that 73% of the children studied were unable to achieve an inspiratory flow greater than 60 litres/minute, and 15% could not achieve 40 litres/minute.

Amirav and Newhouse (2000) found that 30% of the children experienced in the use of the Turbohaler could not achieve 60 litres/minute. Children inexperienced in the use of the device performed even less well. The age above which the optimum peak inspiratory flow could be achieved was 3.5 years for the Accuhaler and 6 years for the Turbohaler. The authors commented that 'Diskus [Accuhaler] usage can be attempted at a younger age than the Turbohaler', and stated that 'it is important to measure peak inspiratory flow in any child who uses a dry powder inhaler or in whom dry powder inhaler use is contemplated, and this can be easily performed with the In-Check Dial device'.

Glaxo Wellcome therefore considered that there was sufficient evidence to support a connection between inspiratory flow rate, drug deposition and clinical effect with respect to dry powder inhalers.

PANEL RULING

The Panel considered that its ruling in Case AUTH/1078/9/00 applied here.

Relevant part of ruling in Case AUTH/1078/9/00: In the Panel's view this [claim] implied that, in contrast, given the bar chart which showed variable doses delivered from the Bricanyl Turbohaler, the Turbohaler might not be efficacious in children and patients with acute asthma. This was not so. A study by Pedersen *et al* noted that 'Virtually all children ≥ 6 years were able to generate an inspiratory flow rate of 30L/min indicating that they would all be able to benefit optimally from Turbohaler treatment'. The Panel noted that the Bricanyl Turbohaler was indicated for use in children. With regard to adults presenting with acute asthma, Glaxo Wellcome cited in its response a paper by Brown *et al* which showed that 50% of such patients might not be able to achieve an inspiratory flow of 60 litres/minute through a Turbohaler, and that 9% might not be able to achieve an inspiratory flow of 40 litres/minute. The Panel noted, however, that the authors of the paper stated that 98% of patients in the study (n=99) generated inspiratory flow through an empty Turbohaler which would allow a therapeutically active amount of a bronchodilator to be delivered to the airways. The Panel noted that the Bricanyl Turbohaler was effective even at low inspiratory flow rates such as those present during an acute asthmatic attack. In the Panel's view, the 'Dear Doctor' letter cast doubt upon the efficacy of the Bricanyl Turbohaler in children and those presenting with acute asthma. The Panel considered that the letter was misleading in this respect and a breach of Clause 7.2 was ruled. The ruling had been accepted by Glaxo Wellcome.

Panel ruling in Case AUTH/1096/11/00: The Panel considered its ruling in Case AUTH/1078/9/00 applied here and a breach of Clause 7.2 was ruled.

This ruling was appealed by GlaxoSmithKline.

6 Claim 'Appreciating the importance of accurate assessment of inspiratory flow rate in allowing you to choose the most appropriate inhaler for your patients ...'

This claim appeared at the start of the postscript to the letter.

COMPLAINT

AstraZeneca referred to the points made at point 2 above, which highlighted the process for choosing the right inhaler device for the patient. Assessment of inspiratory flow rate was not established within current clinical practice as the overwhelming feature in the choice of inhaler device. Indeed personal training and assessment with the device was the feature consistently accepted as good clinical practice. However, this had been neglected in this letter.

Persson *et al* (1997) demonstrated that appropriate inhaler training could optimise the use of the Turbohaler allowing patients to achieve higher inspiratory flow rates, even in severe asthma.

RESPONSE

Glaxo Wellcome stated that nowhere in the material did it state that inspiratory flow was the overwhelming feature in the choice of inhaler device. However, it was clear that it was an important feature as was recognised not only by health professionals and Glaxo Wellcome but also by AstraZeneca as shown by its studies and patient materials. The response to the previous section highlighted some of the important clinical papers on this issue.

Glaxo Wellcome noted that AstraZeneca was aware of the issue of optimal inspiratory flow rate and its relevance to clinical effect. Following the publication of the study of Persson *et al* referred to below, AstraZeneca amended the instructions in the patient information leaflet enclosed with the Turbohaler from 'breath in deeply' to 'breath in as deeply and as hard as you can'. Furthermore, an AstraZeneca study protocol evaluating efficacy of the Turbohaler required that patients should be able to inhale through the Turbohaler at 60 litres/minute, recognising the importance of this optimal inspiratory flow for effective use of the Turbohaler.

Glaxo Wellcome noted AstraZeneca's submission that 'Persson *et al* demonstrated that appropriate inhaler training can optimise the use of the Turbohaler allowing patients to achieve higher inspiratory flow rates, even in severe asthma'. The authors of this study did not evaluate patients according to the severity of their asthma. They did however show that a patient's inspiratory technique could be improved. They reported that 83-84% of patients could achieve >40 litres/minute with the standard instruction of inhale deeply, and that 52-64%, could achieve ≥ 60 litres/minute. When the instruction was changed to 'forceful and deep', only 1-3% of patients failed to achieve 40 litres/minute, however 29-33% of the patients studied were still unable to achieve a flow rate ≥ 60 litres/minute.

Nsour *et al* (1999) evaluated the ability of patients with COPD to use the Turbohaler. They found that

87% could not achieve an inspiratory flow over 60 litres/minute and 31% could not achieve over 40 litres/minute. The authors commented that 'The In-Check measurement highlights the potential of this simple meter as an aid to decide which DPI to prescribe'.

PANEL RULING

The Panel considered that its ruling made in Case AUTH/1078/9/00 and detailed at point 2 above was relevant with regard to the number of factors which could affect the respirable dose. The Panel noted that inspiratory flow rate was one of a number of important issues in determining clinical outcome and choice of inhaler. The Panel considered that the claim at issue was sufficiently broad; it did not state or imply that inspiratory flow rate was the only important factor when choosing an inhaler. No breach of Clause 7.2 was ruled.

7 The offer of free In-Check Dial devices

COMPLAINT

AstraZeneca firmly believed that the current design of the In-Check Dial device misrepresented the ease of use and the clinical benefits derived from the Turbohaler (in relation to other inhaler devices assessed by the In-Check). The In-Check Dial device set inappropriate levels of inspiratory flow rate for the Turbohaler. It specifically implied that the Turbohaler could not be used with inspiratory flow rates of less than 60L/min. This contradicted the balance of clinical evidence as described above. As such, the free offer was misleading and an inducement that unfairly encouraged the recipient to prescribe other devices ahead of the Turbohaler.

AstraZeneca alleged that the above features of the advertisement constituted breaches of Clauses 7.2 and 18.1 of the Code.

AstraZeneca stated that it might be of interest that in a recent case in front of the Swedish Association of the Pharmaceutical Industry, the Information Practices Committee found that GlaxoWellcome had acted in violation of good practice in the area of drug information by using a diagram in its marketing activities that gave the reader an incorrect and misleading representation of the Turbohaler's effects at different inspiratory flows. The diagram in question was the one attached to the In-Check Dial.

RESPONSE

Glaxo Wellcome stated that the optimum flow rates and ranges for drug delivery described on the In-Check Dial were made following consultation by Clement Clarke International with the various companies whose products were represented on the device (including AstraZeneca). In respect of the Accuhaler and the Turbohaler, these inspiratory flow rates were 30-90 litres/minute for the Accuhaler and 60-90 litres/minute for the Turbohaler. Nowhere on the In-Check Dial was it implied that the Turbohaler could not be used with inspiratory flow rates of less than 60 litres/minute.

It should be noted that the device advised on the optimum inspiratory flow rate for a range of devices. Two devices detailed on the device had lower optimum inspiratory flow rate recommendations than the Accuhaler.

Glaxo Wellcome had been informed by Clement Clarke that all the calibrations on the device had been independently validated as accurate by the Aerosol Science Centre at Atomic Energy Authority Technology. This last validation study was provided on a confidential basis.

Glaxo Wellcome did not at any time cast doubt on the efficacy of the Turbohaler but showed a difference in the delivery characteristics of dry powder inhalers. It sought to help ensure that the ability of patients to use particular devices was checked (as advised in the British Thoracic Society guidelines on device selection and the National Asthma and Respiratory Training Centre device selection recommendations) when patients with asthma were reviewed. This was made clear in the representatives' In-Check Dial briefing document. From this document it could be seen that the emphasis was on the importance of checking inhaler device technique over a range of devices, as a part of rounded asthma management, when patients were reviewed.

There was an increasing interest in inspiratory flow as greater understanding of the importance of this aspect of drug delivery had developed. Measurements of inspiratory flow were increasingly forming a part of respiratory studies, and many presentations at national and international meetings highlighted inspiratory flow as an important measurement of lung function. In discussing this aspect of inhaler technique and device selection Glaxo Wellcome was reflecting the growing interest in inspiratory flow resistance.

PANEL RULING

The Panel noted that the In-Check Dial was a device which comprised a low range inspiratory flow meter (15 to 120L/min) that had a selectable resistance calibrated to enable measurement of airflow as if the patient was using the following inhalers; Turbohaler, Accuhaler/Diskus, Autohaler and the Easi-Breathe/Surehaler. The first point the Panel had to consider was whether the matter came within the Code. The Panel noted that the Code applied to the promotion of medicines and not to the promotion of devices *per se*. The Panel noted that the In-Check Dial was provided as a competition prize. The competition formed part of a promotional mailing for the Ventolin Accuhaler. The Panel considered that the provision of the In-Check Dial by Glaxo Wellcome in such circumstances came within the scope of the Code.

The Panel noted that a table which appeared on a card accompanying the In-Check Dial, headed 'Optimum Inspiratory Flow', showed the inspiratory flow rates for the Accuhaler at 30-90L/min, Turbohaler 60-90L/min, Autohaler 30-60L/min and Easi-Breathe at 20-60L/min. Similar information appeared on the In-Check Dial itself without the reference to 'Optimum Inspiratory Flow' and using symbols for the different types of inhalers.

The Panel noted Glaxo Wellcome's submission that nowhere was it implied that the turbobaler could not be used with inspiratory flow rates of less than 60L/min.

The Panel considered that the ruling at point 5 above was particularly relevant here with regard to the effectiveness of the Turbobaler at low inspiratory flow rates in children and those presenting with acute asthma. The Panel considered that given its rulings above on the content of the 'Dear Doctor' letter, the table of inspiratory flow rates on the In-Check Dial created the impression, in conjunction with the 'Dear Doctor' letter, that the Turbobaler could not be used at all with inspiratory flow rates of less than 60L/min. In this regard the Panel considered that the use of the In-Check Dial device as a prize in a promotional competition by Glaxo Wellcome was misleading and a breach of Clause 7.2 was ruled. The Panel considered that the alleged breach of Clause 18.1 was covered by this ruling.

The ruling of a breach of Clause 7.2 was appealed by GlaxoSmithKline.

APPEAL BY GLAXOSMITHKLINE

GlaxoSmithKline (which Glaxo Wellcome had by then become) appealed the rulings of breaches of the Code at points 5 and 7.

General Points

GlaxoSmithKline considered that it should appeal as the importance and clinical relevance of inspiratory flow to the evaluation of dry powder inhaler devices had been accepted and commented on by authorities such as the British Thoracic Society (BTS), the National Institute for Clinical Excellence (NICE), the European Agency for the Evaluation of Medicinal Products and the Drug and Therapeutics Bulletin as well as by health professionals.

The basis of the appeal was to show that AstraZeneca itself accepted the clinical relevance of the flow dependent delivery of the Turbobaler and that this relevance was also accepted by authorities and expert opinion, and supported by clinical studies.

GlaxoSmithKline stated that it then intended to demonstrate that in the commonly understood meaning of the word, 'optimum' was a reasonable interpretation of the data available, which taken in the context of the meaning of optimum, would not lead someone to interpret that there was only effect within the optimum range.

GlaxoSmithKline considered that no statements or claims within the material would lead a health professional to believe that the Turbobaler was ineffective at flow rates below 60 litres/minute.

GlaxoSmithKline would demonstrate that the In-Check Dial device was an appropriate means by which to check the inspiratory flow component of inhaler device technique.

GlaxoSmithKline did not challenge any of the SPC for the Turbobaler, but asserted that it was reasonable to discuss degrees of effectiveness for any product which had a dose response relationship.

GlaxoSmithKline accepted that there was a statement in the SPC for Bricanyl Turbobaler relating to its effectiveness in adults and children with acute asthma. However, it would seem that such a statement should not preclude a comparison of degrees of effectiveness, as long as there was no implication that a product was ineffective. This principle would seem to apply to all products; that as long as the product had a dose response curve, clinical response would vary according to delivered dose. This principle was accepted by both health professionals and pharmaceutical companies.

Whilst GlaxoSmithKline referred to terbutaline turbo inhaler, it considered that reduced drug delivery was also clinically important with preventative medications such as inhaled steroids, as well as reliever medications such as terbutaline.

With inhaled steroids, if asthma was deteriorating and the patient was unable to get the full benefit from the inhaler, there would be no rapid feedback in terms of reduced efficacy as there might be with a β_2 agonist (such as terbutaline), and the deterioration might continue, with the patient continuing to obtain a reduced dose of the drug from the inhaler.

GlaxoSmithKline noted that until this complaint, AstraZeneca accepted the principle and clinical relevance of optimal use of the Turbobaler. AstraZeneca still applied this principle in its SPCs, patient information leaflets (PILs), websites, study criteria and training materials. AstraZeneca acknowledged the principle and use of optimum (or optimal) inspiratory flow rate and its relevance to the clinical effect of the Turbobaler.

GlaxoSmithKline noted that the SPCs for both 6mcg and 12mcg Oxis Turbobalers (which were licensed after the publication of the Persson paper detailed below) stated in section 6.6: 'Note. It is important to instruct patients to breathe in forcefully and deeply through the mouthpiece to ensure that an optimal dose is obtained'.

An AstraZeneca study by Persson *et al* showed that a patient's inspiratory technique when using the Turbobaler could be improved, and that there was a variation in the ability of patients to achieve particular flow rates. The authors reported that 83-84% of patients could achieve >40 litres/minute with the standard instruction of inhale deeply, but that only 52-64% could achieve ≥ 60 litres/minute. However, when the instruction was changed to 'forceful and deep', 67-81% could achieve ≥ 60 litres/minute.

The authors commented: 'This study demonstrates that instructing a patient to take a 'forceful and deep' inhalation optimises the use of Turbobaler'.

Following the publication of this study, AstraZeneca amended the instructions in the patient information leaflet enclosed with the Turbobaler from 'breathe in deeply' to 'breathe in as deeply and as hard as you can'.

AstraZeneca further stated in its letter of complaint that 'Persson demonstrated that appropriate inhaler training can optimise the use of the Turbobaler allowing patients to achieve higher inspiratory flow rates, even in severe asthma'. This statement

demonstrated awareness that the Turbohaler could be used optimally if high inspiratory flows were used.

AstraZeneca's website acknowledged the effect that inspiratory flow had on the performance of its device. Last year a statement on the function of the Turbohaler read: 'Turbohaler works optimally at a fast inhaled flow rate, but functions adequately at a lower flow rate ie 30L/min'. An update in January 2000 had omitted the word 'optimally' from the text although it still appeared in the reference cited (Newman *et al* 1991). However, the section on the website currently retained the word optimally.

A separate AstraZeneca website contained a slide set on the Turbohaler. Under Disadvantages of the Turbohaler one of the slides included the statement: 'Inspiratory flow-dependent (potential problem at low inspiratory force).

GlaxoSmithKline stated that AstraZeneca had presented studies in support of the use of a reduced dose of budesonide when delivered via the Turbohaler compared to the metered dose inhaler. This recommendation was based on the increased deposition achieved via the Turbohaler when used optimally. However, patients entering the trial had to be able to achieve 60L/min to be included in the study, the study report methodology stating 'The subjects were trained to ... inhale at a flow of 60L/min for Turbohaler', recognising the importance of this inspiratory flow for optimal use of the Turbohaler.

An Astra study stated 'The flow rate attained by a patient depends on the effort expended and on the air flow resistance of the device. A comparison between powder inhalers should therefore take their air flow resistances into account'.

A recent AstraZeneca leaflet reinforced this by quoting the increased deposition achieved at a flow rate of 60L/min. However, the same leaflet showed that at a reduced flow rate of 30L/min through the Turbohaler less deposition was achieved (the same deposition as was achieved as through a metered dose inhaler).

As AstraZeneca recommended that the dose of budesonide should be reduced when the Turbohaler was used optimally, then this was evidence that it accepted that a change in inspiratory flow could affect clinical outcome.

Training devices for inhaler devices had been around for some time. Many health professionals used the Aerosol Inhalation Monitor (AIMS) machine for teaching the correct use of metered dose inhalers (MDI). The machine consisted of a dummy MDI that was attached to a box of electronics with three lights. When the correct inhalation technique was applied to the dummy metered dose inhaler all three lights illuminated. AstraZeneca produced, recommended for clinical practice and supplied to practices through its representatives, such a device, the 'Turbohaler Usage Trainer'. The patient was instructed to inhale through the dummy Turbohaler, with the effectiveness of the inhalation being judged by the illumination of one or more lights. If the patient only achieved one light ($\geq 30\text{L}/\text{min}$) they were informed that 'it could probably be better'. If they achieved two lights

($\geq 40\text{L}/\text{min}$) they were informed that it was 'a good inhalation but ... it could be even better'. On each occasion they were advised to try again until three lights were achieved. When all three lights were illuminated this was advised to be a 'very good inhalation'. This happened only when an inspiratory flow equal to, or greater than, 60L/min was applied to the Turbohaler. The recognition by AstraZeneca of the relevance of inspiratory flow to clinical effect was surely supported by its promotion of this device.

GlaxoSmithKline concluded that AstraZeneca acknowledged and publicised the fact that device technique and inspiratory flow had a clinical impact on Turbohaler use, and even pointed out on one of its websites that the inspiratory flow dependence of the Turbohaler was a potential problem at low inspiratory force.

Independent bodies and health professionals specialising in the management of respiratory disease accepted as clinically important the relevance of inspiratory flow resistance and optimum inspiratory flow in device evaluation. It had been accepted and understood for many years that the effort a patient put into inspiring through a dry powder inhaler device might affect the dose of drug that was delivered and that this in turn was likely to affect clinical outcome.

Dry powder inhalers used energy, generated within the device during inhalation, to promote dispersion and de-aggregation of the powder, thus producing particles of respirable size (between 2 and 5 microns). The level of energy generated inside each dry powder inhaler, from a set inhalation rate, was dependent on the resistance in the device.

As inspiratory effort was proportional to inspiratory flow rate multiplied by the device resistance, it was easier to generate a given inspiratory flow through a device with low internal resistance than through one with high internal resistance. Richards showed that to achieve a flow of 60 litres/minute through the Turbohaler, three times the inspiratory effort was needed compared with the Diskhaler. He suggested that there should be a comparative performance standard for the evaluation of dry powder inhalers. Andersen found that the majority of patients preferred to inhale from a device with a lower internal resistance than from a device with a high resistance. Comparing six dry powder inhalers, Assi and Chrystyn showed the Turbohaler to be a high resistance device and commented: 'Due to the different resistance in dry powder inhalers the inhalation rate for a set inspiratory effort varies'.

NICE had produced a report on the clinical and cost-effectiveness of inhaler devices for children with chronic asthma. In the section on dry powder inhalers it stated 'The inhaler technique of the Turbohaler [sic] must be considered especially in children as this will have a significant bearing on efficacy. The Turbohaler [sic] has a high internal resistance and needs a relatively high inspiratory flow of 60 litres/minute for optimal drug delivery. This may not be achievable in young children even if it is assumed that the patient is taught to use the device and this factor is known to the teacher'. It

commented on a paediatric asthma study. It also stated 'Other work by Agertoft, in a filter study comparing pMDI + Nebuhaler vs Turbohaler showed that in younger children within the trial, Turbohaler drug delivery was less efficient'.

Advising on dry powder inhalers the BTS in its Guidelines on Asthma Management stated 'there are variations in deposition ranging from 10% to 30%. Inspiratory flow rates also cause variation with the same device'. The European Agency for the Evaluation of Medicinal Products stated in its Note for Guidance on Dry Powder Inhalers (DPIs) 'It is characteristic of DPIs that their design influences the air flow resistance of the device and the airflow achieved by the patient'. Everard *et al* evaluating the Turbohaler stated 'inspiratory flow and the flow profile should be considered when assessing any dry powder inhaler'. Pearce, in a presentation to The Aerosol Society, highlighted the importance of appreciating the differences in inspiratory flow resistances when evaluating and instructing patients in the use of inhaler devices. AstraZeneca itself supported this view when it stated 'The flow rate attained by a patient depends on the effort expended and on the air flow resistance of the device. A comparison between powder inhalers should therefore take their air flow resistance into account'. It was thus generally accepted that internal resistance and inspiratory flow rate were important aspects of dry powder inhalers and should be considered in device selection.

In vitro studies showed that there was an association between inspiratory flow and lung deposition with the Turbohaler, and *in vivo* studies showed the clinical relevance of these findings. *In vitro* studies evaluating the Accuhaler and studies comparing the Accuhaler with the Turbohaler had shown that the Accuhaler delivered a consistent fine particle fraction at a range of flow rates between 30 and 90 litres/minute, whereas with the Turbohaler drug delivery was flow dependent across this range. Indeed, it had been shown that the maximal inspiratory flow rates generated by young asthmatic children might be insufficient for effective operation of high resistance dry powder inhalers. Flow dependent delivery from the Turbohaler was accepted by both AstraZeneca and health professionals, supported by numerous peer-reviewed publications.

The clinical relevance of inspiratory flow was supported by the following *in vitro* studies.

Neilsen *et al* evaluated the clinical effect of the Accuhaler at low and high flow rates in children. They concluded 'consistent *in vitro* fine particle dosing from the Diskus (Accuhaler) inhaler translates into consistent clinical effect at low and high flow rates in children'. In an AstraZeneca study on the Turbohaler Borgstrom *et al* stated 'Our results indicate a direct relationship exists between PIF (peak inspiratory flow) through Turbohaler and lung deposition'. 'Drug deposition in the lungs at 36L/min is at least as good with Turbohaler as with a correctly used pressurised MDI based on this study and a previous study ...'. 'Since lung deposition of budesonide inhaled via a Turbohaler at a PIF of 60L/min is about twice that from a pressurised MDI, patients who generate flows

of about 60L/min may reduce their prescribed dose of budesonide without reducing therapeutic efficacy.' This conclusion asserted that the effectiveness of the Turbohaler at 36L/min was clinically inferior to that at 60L/min since patients who could not achieve 60L/min should not be reducing their dose.

Hirsch *et al* evaluated the effectiveness of bronchodilatation with terbutaline delivered through the Turbohaler in 118 children with asthma. They found significant differences in bronchodilatation which correlated with inspiratory flow. The authors concluded that 'When using the Turbohaler for bronchodilatation, the effectiveness of terbutaline depends upon the degree of inspiratory capacity. This can lead to impaired bronchodilatory effect in subgroups of obstructive young asthmatics with low inspiratory flow. In contrast when using a pMDI, inspiratory capacity did not seem to influence the effectiveness of terbutaline'.

Engel *et al* compared the clinical effectiveness of budesonide delivered via the Turbohaler and the pressurised metered dose inhaler in terms of lung function and bronchial hyper-responsiveness. They measured, among other parameters, bronchial hyper-responsiveness which was a measure of the sensitivity of the airways to eg allergic stimuli, and was reduced in patients treated with inhaled corticosteroids. It was regarded as a measure of the anti-inflammatory effect of inhaled steroids. An increased level of bronchial hyper-responsiveness reflected decreased anti-inflammatory effect (reduced protection) for a medication. The study showed that although FEV1 results were similar at different flow rates, they found that bronchial hyper-responsiveness was increased at low flow rates compared with high flow rates through the Turbohaler. The authors concluded 'one of the crucial points in inhaling through dry powder inhalers was the peak flow generated during the inhalation'.

Amirav and Newhouse found that 30% of the children experienced in the use of the Turbohaler could not achieve 60 litres/minute. Children inexperienced in the use of the device performed even less well. The age above which the optimum peak inspiratory flow could be achieved was 3.5 years for the Accuhaler and 6 years for the Turbohaler. The authors commented that 'Diskus (Accuhaler) usage could be attempted at a younger age than the Turbohaler' and stated that 'it is important to measure peak inspiratory flow in any child who uses a dry powder inhaler or in whom dry powder inhaler use is contemplated, and this can be easily performed with the In-Check Dial device'.

An AstraZeneca paediatric study found an age dependent increase in ability to use the Turbohaler with considerable scatter across age groups, and concluded that the dose delivered could not be predicted in young children. Discussing the Turbohaler the authors concluded that they 'are not reliable in all circumstances for treatment of young children, and careful and repeated tuition is required if such devices are to be used'.

It should be noted that without a measurement of inspiratory flow as part of the tuition process, there was no way of ensuring that the patient could achieve optimum (or even effective) technique.

De Boeck *et al* evaluated the ability of children with asthma to use a Turbohaler. They found that 73% of the children studied were unable to achieve an inspiratory flow greater than 60 litres/minute, and 15% could not achieve 40 litres/minute.

Pedersen *et al* evaluated the influence of inspiratory flow resistance on the effect of a Turbohaler in children. AstraZeneca used this study to support its complaint. However, in the complaint AstraZeneca incorrectly commented on the study findings when it stated that 'the beneficial clinical effects of the Turbohaler were retained down to inspiratory flow rates of 30L/min'. The conclusion was not stated by the authors of the study and was not supported by the study results. What the authors did state was that 'Virtually all children ≥ 6 years were able to generate an inspiratory flow rate of 30L/min indicating that they would all be able to benefit optimally from Turbohaler treatment'. It was important to note that in the same paragraph, the authors went on to state 'About a quarter of children aged 3-5 years, however, could not generate this inspiratory flow rate under basic conditions. Further this number was even higher during attacks of acute bronchospasm or in periods of poor control of symptoms'. In this paper Pedersen *et al* actually reported that 26% of children under six years and 60% of children with acute wheeze could not generate an inspiratory flow rate of 30L/minute. The authors concluded 'Young children may gain less benefit from the treatment [Turbohaler] because they cannot generate sufficiently high inspiratory flow rates, especially during episodes of acute bronchoconstriction. This may also be true for a few older children during episodes of acute wheeze'.

Although the Panel ruling focussed on the author's comment on children ≥ 6 years, it should be noted that both the Bricanyl and Pulmicort Turbohalers were licensed for use in younger children, and therefore it was important that the ability of this age group to use the Turbohaler should be evaluated.

AstraZeneca also incorrectly commented upon a further study in adults by Brown *et al*. AstraZeneca stated in its letter of complaint 'that Brown demonstrated in a study of 99 patients attending with acute asthma that 98% generated an inspiratory flow rate of 30 litres/minute'. This was not demonstrated by this study. The authors of this study, which was sponsored by AstraZeneca, in fact reported that 9% might not be able to achieve an inspiratory flow of 40 litres/minute. If the data were analysed it could be seen that 50% of adults in this study were not able to achieve an inspiratory flow of 60 litres/minute through the Turbohaler. It was important to realise that this was not a study of clinical effectiveness as no terbutaline was inhaled to assess the actual clinical effect on patients. This study was performed using an empty Turbohaler.

Nsour *et al* evaluated the ability of patients with COPD to use the Turbohaler. They found that 87% could not achieve an inspiratory flow over 60 litres/minute and 30% could not achieve over 40 litres/minute. The authors commented that 'The In-Check measurement highlights the potential of this simple meter as an aid to decide which DPI (dry powder inhaler) to prescribe'.

Whilst GlaxoSmithKline freely acknowledged there would be clinical benefit at lower flows than 60L/min, there seemed ample clinical evidence, when taken together with *in vitro* studies on dose variability at low flows, to show that 30L/min was not the optimal inspiratory flow rate for the Turbohaler. GlaxoSmithKline's use of these studies to defend against the complaint did not challenge the fact that the Turbohaler was effective at lower flow rates, only that the level of effectiveness might vary according to the inspiratory flow generated. This was supported by the review of the Drug and Therapeutics Bulletin, Inhaler Devices for Asthma. Referring to the Turbohaler, the authors stated 'However, the dose of drug delivered and the amount reaching the lungs falls by 5% at inspiratory flow rates of 30 - 40L/min and the dose that can be inhaled by children up to 8 years old varies widely'.

GlaxoSmithKline restated its acceptance of the data sheet/SPC for Bricanyl Turbohaler relating to its effectiveness in adults and children with acute asthma. However, again it would seem that a licence for a particular indication should not preclude a comparison of degrees of effectiveness for a product. In GlaxoSmithKline's material it stated 'This (inspiratory flow) may be important in children and patients whose asthma is deteriorating, who may have low inspiratory flow rates'. The studies quoted above and the conclusions of their authors summarised below, supported this statement.

'When using the Turbohaler for bronchodilatation, the effectiveness of terbutaline depends upon the degree of inspiratory capacity. This can lead to impaired bronchodilatory effect in subgroups of obstructive young asthmatics with low inspiratory flow' (Hirsch).

'Young children may gain less benefit from the treatment [Turbohaler] because they cannot generate sufficiently high inspiratory flow rates, especially during episodes of acute bronchoconstriction. This may also be true for a few older children during episodes of acute wheeze.' (Pedersen).

'Our results indicate that dry powder inhalers are not reliable in all circumstances for treatment of young children, and that careful and repeated tuition is required if such devices are to be used.' (Bisgaard).

'One of the crucial points in inhaling through dry powder inhalers is the peak flow generated during the inhalation.' (Engel).

GlaxoSmithKline considered that there was sufficient evidence to support a connection between inspiratory flow rate, drug deposition and clinical effect with respect to dry powder inhalers. It submitted that it was not inappropriate to draw attention to these issues, and denied that it anywhere suggested that the Turbohaler could not be used or was ineffective at reduced flow rates.

The use of the word optimum (or optimal) did not imply exclusivity, but the best result. The use of the word 'optimum' was critical in the application of the In-Check Dial; it did not imply that any device did not work at other flow rates. The Collins English Dictionary defined optimum as a condition, degree amount or compromise that produces the best

possible result and as most favourable or advantageous use.

In the commonly understood meaning of the word, optimum was a reasonable interpretation of the data available. Taken in the context of the meaning of optimum, the data and claim would not lead someone to interpret that there was only effect within the optimum range. That is, it would not lead someone to interpret that there was only effect within the stated range of peak inspiratory flow rates, but that the drug delivery of the device and hence the clinical effectiveness of the product (drug and device) was optimised within this range.

GlaxoSmithKline's briefing materials for use with the In-Check Dial did not anywhere state or imply that the Turbohaler was ineffective. GlaxoSmithKline stated that it did not at any time seek to cast doubt on the efficacy of the Turbohaler, but to show a difference in the delivery characteristics of dry powder inhalers. It sought to help ensure that the ability of patients to use particular devices was checked. Both the BTS and the NARTC advised that device technique was checked, both at review and when selecting inhaler devices. This advice was made clear in the representatives' In-Check Dial briefing document. From this document, it could be seen that the emphasis was on the importance of checking inhaler device technique over a range of devices, as a part of rounded asthma management when patients were reviewed. The document clearly stated 'For a variety of reasons there is no one ideal device for all patients and it was important to match a device to the individual patient's current needs. It was important to recognise that over time a patient's needs might change. The In-Check Dial offered health care professionals a tool to check a patient's suitability for a particular device'. These statements showed that GlaxoSmithKline was careful not to state that any device was ineffective, but suggested that device technique checking was an important aspect of clinical management. The NARTC, the main training body for respiratory nurses in the UK, supported this approach.

The BTS guidelines also emphasised the importance of inhaler device technique and selection stating that 'The most common reason for failure of inhaled drugs in children is inappropriate selection or incorrect use of an inhaler'.

There was an increasing interest in inspiratory flow as greater understanding of the importance of this aspect of drug delivery had developed. Measurements of inspiratory flow were increasingly forming a part of respiratory studies, and many presentations at national and international meetings highlighted inspiratory flow as an important measurement of lung function. In discussing this aspect of inhaler technique and device selection, GlaxoSmithKline aimed to reflect the growing interest in inspiratory flow resistance.

The In-Check Dial had been independently validated using flow ranges that were discussed with all manufacturers concerned. The In-Check Dial materials used the word 'optimum'. The In-Check Dial was an independently validated tool by which assessments of inhaler technique and patient inhaler

device training might be carried out.

GlaxoSmithKline had been informed by Clement Clarke that all the calibrations on the device had been independently validated as accurate by AEA Technology. The In-Check Dial had also been evaluated and correlated with electronic measurement of peak inspiratory flow rate independently by Tarsin *et al* and found to be accurate. The optimum flow rates and ranges for drug delivery described on the In-Check Dial were made following consultation by Clement Clarke with the various pharmaceutical companies whose products were represented on the device (including AstraZeneca). In addition, Clement Clarke also reviewed the literature, and consulted with clinicians knowledgeable in the subject area.

It should be noted that the device only advised on the optimum inspiratory flow rate for a range of devices and that two inhaler devices detailed on the In-Check Dial had lower optimum inspiratory flow rate recommendations than the Accuhaler. In respect of the Accuhaler and the Turbohaler, these optimum inspiratory flow rates were 30 - 90 litres/minute for the Accuhaler and 60 - 90 litres/minute for the Turbohaler. Nowhere on the In-Check Dial was it implied that the Turbohaler could not be used with inspiratory flow rates of less than 60 litres/minute.

The use of the word optimum in the Clement Clarke materials accompanying the In-Check Dial, did not infer lack of efficacy, but reflected AstraZeneca's advice on use of the Turbohaler, and the materials it used to support Turbohaler use and device assessment. GlaxoSmithKline considered that the In-Check Dial offer, viewed in the light of the representative's briefing document on this device, was not in breach of Clause 7.2 of the Code.

Since AstraZeneca had made mention of the recent ruling in a case before the Swedish Association of the Pharmaceutical Industry (NBL), GlaxoSmithKline considered that the following information passed on to it by Clement Clarke, although not revealed by AstraZeneca in its complaint, might put this related ruling into context. AstraZeneca had complained about a diagram that accompanied the In-Check Dial, using the English language title. AstraZeneca cited the word 'Optimum' as misleading. The NBL ruling found (translated from the Swedish) 'The diagram which is the subject of complaint is dominated by the horizontal graph and the heading 'Optimum Inspiratory Flow'. It is the decision of the NBL it cannot be assumed that the meaning of the term 'Optimum Inspiratory Flow' would be entirely clear to a Swedish-speaking reader'. At no point did AstraZeneca reveal to the NBL that Clement Clarke included a full explanation of the In-Check Dial and the importance of 'Optimum Inspiratory Flow' in Swedish, in the booklet that accompanied the device. GlaxoSmithKline considered that the judgement might have been prejudiced through AstraZeneca's non-disclosure of the translation (required under CE regulations) that accompanied every In-Check Dial. Clement Clarke was only alerted to the Swedish ruling after the case had been heard, and despite lengthy and detailed requests, the NBL had refused to reconsider the ruling. Clement Clarke had noted that the NBL had no appeal procedure and no statute for appeal.

GlaxoSmithKline appealed two of the findings of the Panel.

5 Claim '[Dose consistency] may be important in children and patients whose asthma is deteriorating, who may have low inspiratory flow rates'.

GlaxoSmithKline considered that this statement was true. Consistency of dose in children and patients whose asthma was deteriorating was relevant to clinical practice.

Studies from AstraZeneca and from independent researchers had concluded that there was *in vitro* dose variability and associated variability of clinical response with the Turbohaler. This dose variability and the concept of an 'optimal' inspiratory flow rate was accepted by AstraZeneca in its SPCs, website, studies and promotional materials.

Conclusions of the authors of clinical studies stated their belief in the clinical relevance of dose variability through the Turbohaler.

APPEAL BOARD RULING

The Appeal Board noted that Section 6.6 of the SPCs for the Oxis Turbohalers (6mcg and 12mcg) advised the prescriber that it was important to instruct the patient to breathe in forcefully and deeply through the mouthpiece to ensure that an optimal dose was obtained. The Appeal Board further noted GlaxoSmithKline's submission that AstraZeneca had amended the instructions in the Turbohaler PIL from 'Breathe in deeply' to 'Breathe in deeply and as hard as you can'.

The Appeal Board noted the data from both parties. It noted that the claim was that consistency of dose may be (emphasis added) important in children and patients whose asthma was deteriorating and who may have low inspiratory flow rates. The Appeal Board did not consider that the claim was unreasonable and therefore ruled no breach of Clause 7.2 of the Code. The appeal on this point was successful.

7 The offer of free In-Check Dial devices

GlaxoSmithKline stated that its briefing materials made it clear that this device was to be used as a teaching, training and technique checking aid.

It stated 'For a variety of reasons there is no one ideal device for all patients and it is important to match a device to the individual patient's current needs. It is important to recognise that over time a patient's needs may change. The In-Check Dial offers health care professionals a tool to check a patient's suitability for a particular device'.

GlaxoSmithKline was clearly endeavouring to ensure that its representatives promoted the use of this device in an ethical manner.

The device itself, which had been independently produced and validated, measured a patient's inspiratory flow rate in order to assist in teaching

inhalation technique and assess the patient's ability to achieve the optimum inspiratory flow through one of four or five devices. The instructions with the In-Check Dial clearly stated that the device measured the optimum inspiratory flow rate for a device.

The GlaxoSmithKline representatives explained that there was concern about the undertaking required to be given that GlaxoSmithKline could not use the In-Check Dial promotionally. The In-Check Dial had been distributed as a promotional aid by its medical representatives.

APPEAL BOARD RULING

The Appeal Board noted that the offer of the In-Check Dial in the 'Dear Doctor' letter promoting Ventolin Accuhaler meant that the provision of the In-Check Dial was within the scope of the Code. This was not disputed by GlaxoSmithKline.

The Appeal Board noted that the In-Check Dial itself had a label which ran along its length. The top edge of the label was marked from 15-120L/min with graduations at every 5L/min. Beneath this scale symbols depicting four different inhalation devices were shown (Accuhaler, Turbohaler, Autohaler and Easi-Breathe) and for each device a green band was shown. The green band for Turbohaler started at 60L/min and finished at 90L/min. There was no explanation on the label as to what the symbols for each inhaler device represented or how the green bars for each inhaler device should be interpreted.

The In-Check Dial was accompanied by a booklet which gave instructions as to its use in English and 12 other languages. A laminated card headed 'Optimum Inspiratory Flow' was also provided. Beneath the heading on the card, in similar but not identical format, was a copy of the label which was on the In-Check Dial itself. The card had more information than the labelling on the In-Check Dial. It was only by reference to the instruction booklet and the laminated card that the labelling of the In-Check Dial itself was explained. The Appeal Board noted that in practice the In-Check Dial would eventually become separated from any accompanying explanatory item. GlaxoSmithKline had stated that the use of the word optimum was critical in the application of the In-Check Dial.

The Appeal Board considered that the information on the In-Check Dial itself without further explanation implied that only patients with an inspiratory flow rate of between 60 and 90L/min could use the Turbohaler and that was not so. The range for the maximum effect was 60-90L/min. The Appeal Board considered that the inadequate labelling on the device itself was such that its use for a promotional purpose was misleading. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful. The laminated card was not considered.

Complaint received	14 November 2000
Case completed	23 April 2001

ABBOTT v ROCHE

Promotion of Fortovase and Viracept and conduct of representatives

Abbott complained about six items produced by Roche in relation to the HIV therapeutic area and also alleged unprofessional behaviour by a Roche representative in relation to Abbott's developmental protease inhibitor ABT-378/r (lopinavir/ritonavir).

Abbott stated that a special report on a resistance workshop was prominently displayed and freely available on the Roche stand at an HIV Pharmacy Association meeting. Beneath a header of 'Good to hear that they were thinking of their patients' appeared the statement: 'The meeting was really left up on [sic] the air as to the effectiveness of ABT against virus with resistance mutations. No one really knew'. Abbott stated that no scientific rationale was provided and the lasting impression would be to cast doubt as to the effectiveness of ABT-378/r against resistant virus. The same page contained the statement: '... Canadian physicians who were all saying 'buy, buy, buy' and then after the questions they were saying 'sell, sell, sell'. Abbott alleged that these statements disparaged ABT-378/r and the company respectively.

The Panel noted that the report was freely available on the Internet, published by the National AIDS Manual (NAM), an independent organisation that provided scientific and medical information to people living with HIV and to healthcare professionals. It appeared to be a verbatim report of an interview with an HIV physician; it was not written in scientific language and contained only the unchallenged opinion of the interviewee. Although Roche had provided donations to NAM it had not sponsored or otherwise influenced the content of the report. The Panel considered that the independent report had been used by Roche for a promotional purpose. In intercompany correspondence Roche had stated that the report was photocopied by one of its representatives and had not been certified. The Panel ruled a breach as the representative, by supplying material which had not been approved for promotional use by the company, had failed to maintain a high standard of ethical conduct and had not complied with the relevant requirements of the Code. A breach was also ruled as the report disparaged Abbott and ABT-378/r.

Abbott stated that a booklet on key developments in protease inhibitors was openly displayed and freely available at the Roche stand at a British HIV Association (BHIVA) meeting. It contained a review of selected abstracts by an expert panel. Abbott believed that the fact that an 'independent panel of experts' reviewed the abstracts was irrelevant. The booklet was commissioned by Roche; it was of 'glossy' non-scientific appearance, and the manner in which it was distributed was promotional. As such, prescribing information should have been included. Abbott did not consider that references to pharmacokinetic benefits of twice-daily dosing of Roche's product nelfinavir, contrary to the current product licence, and to Abbott's unlicensed product, were acceptable in a promotional item. Furthermore, reference to the off-licence use of nelfinavir was not brought to the attention of clinicians attending this UK meeting. Abbott believed that this item represented disguised promotion.

The Panel noted that the booklet was a review of selected abstracts from the 40th Interscience Conference on Microbial Agents and Chemotherapy which provided an overview of current thinking regarding protease inhibitors. The report stated that it had been made possible by an educational grant from Roche and had been distributed in accordance with the company's wishes. Three abstracts referred to the twice-daily dosing of nelfinavir (Roche's product Viracept, so licensed in the USA but licensed for three times daily dosing in the UK) and two abstracts referred to Abbott's unlicensed product ABT-378/r. The Panel considered that the booklet was a promotional item. It had a glossy, colourful front cover. Roche had briefed the publisher with regard to the selection of the abstracts – there were fifteen and all but one of them mentioned Roche's products in the abstract or its associated comments. Roche had submitted that the booklet was available on request only and that a copy on the stand made this clear. Copies of labels provided by Roche read 'Stand copy only – please request a copy from the Roche Stand Representative'. The Panel considered that such requests for the booklet could not be regarded as unsolicited; by providing a copy of the booklet and placing such a notice on it Roche was in effect soliciting such requests. The booklet was subtitled 'A review of selected abstracts by an expert panel' and the Panel considered that some readers might assume that the abstracts had been chosen by the expert panel whereas in fact they had been chosen by Roche and for the most part mentioned its products. Readers had not been provided with sufficient explanations about the company's role in the selection of the abstracts. The Panel ruled that the booklet was disguised promotion in breach of the Code. The abstracts referred to Roche's products but prescribing information was not provided and a breach of the Code was ruled in that regard. Some of the abstracts referred to the use of nelfinavir (Viracept) twice-daily which was not in accordance with its UK marketing authorization. A further breach of the Code was ruled.

Abbott stated that a reply paid card was prominently displayed and freely available on the Roche stand at a BHIVA meeting. It was designed to record physician interest in company products and enquiries were passed to the medical department for further action. The card contained reference to off-licence use of both nelfinavir and saquinavir and it was clearly inviting requests for information that fell beyond the marketing authorizations for both products. In the absence of a specific medical enquiry, Abbott believed that it was inappropriate to have pre-printed cards freely available on a promotional stand that invited enquiries about the unlicensed use of a product.

The card did not allow for any enquiry other than those the company had detailed on the card. Abbott believed that use of cards in this manner was a practice that effectively solicited information requests.

The Panel noted that the reply paid card allowed information to be requested on nelfinavir in high viral loads; twice-daily nelfinavir; saquinavir with mini-dose ritonavir and once-daily saquinavir soft capsule. According to the relevant summaries of product characteristics (SPCs), Viracept (nelfinavir) and Fortovase (saquinavir) were both only licensed for use three times daily. The Panel accepted that some people would be interested in alternative dosing schedules for each product but considered that by referring to such uses on a reply paid card Roche was soliciting enquiries and in effect promoting use of the products in a way which was inconsistent with their respective SPCs. A breach of the Code was ruled. The Panel did not consider that the reply paid card represented disguised promotion and no breach of the Code was ruled.

Abbott stated that a post conference scientific slide service was also prominently displayed and freely available on the Roche stand at a BHIVA meeting. It was a pre-prepared collection of slides relating to various clinical trials involving Roche's products, including nelfinavir at a twice-daily dose which was not consistent with the current product licence. Abbott alleged that the reference to off-licence use of nelfinavir was inappropriate and that prescribing information should have been included. Abbott believed that this represented disguised promotion.

The Panel noted that the item was a catalogue containing pictures of 78 slides which detailed a number of separate studies, all of which had involved the use of Roche's products nelfinavir or saquinavir. One of the studies reported the use of twice-daily nelfinavir and the conclusion slide for that study stated that '... BID nelfinavir is equally effective to TID nelfinavir during 96 weeks of therapy'. A statement on the front cover read 'To order an individualised slide set on PowerPoint format, select required slides from this catalogue and complete the accompanying request form'. It was stated that the service was provided by the Drug Information Department. The Roche logo was on the back cover. The Panel considered that the slide catalogue was a promotional item. All of the studies detailed had involved the use of one of Roche's products and the item had been made available on the company's stand at a BHIVA meeting. The Panel considered that some readers might assume that it contained details of slides of all the presentations at a conference whereas in fact each study included involved one of Roche's products. The Panel noted that the catalogue and the individual slides were available on request only but considered that such requests were not unsolicited; Roche's provision of the item on its stand was in effect soliciting such requests. The Panel considered that it amounted to disguised promotion and a breach of the Code was ruled. Some of the slides referred to the use of nelfinavir (Viracept) twice-daily which was not in accordance

with its UK marketing authorization. Viracept was licensed for use three times daily in the UK. A breach of the Code was ruled in that regard also.

Abbott stated that a booklet of selected abstracts on nelfinavir was prominently displayed and freely available on the Roche stand at a BHIVA meeting. It contained numerous abstracts pertaining to nelfinavir, both in currently licensed (tds) and unlicensed (bd) dosing frequencies. Attention was not drawn to the currently unlicensed status of bd nelfinavir. Abbott claimed that the reference to off-licence use of nelfinavir was inappropriate, and that it should have included prescribing information. Abbott believed this item was used in a promotional manner and it represented disguised promotion.

The Panel noted that the booklet contained a number of abstracts detailing the efficacy of nelfinavir and discussing the implications for future treatment. Some of the abstracts referred to saquinavir (Fortovase). Use was made of boxed text to highlight important points. The conclusion 'box' of an abstract detailing the results of a trial which had compared the use of nelfinavir bd and tds stated that both dosing schedules were equally effective during 96 weeks of therapy and that both showed a consistent, long-term improvement in cell count. The Panel considered that the abstracts booklet was a promotional item and that requests for the booklet could not be regarded as unsolicited – by providing a copy of the booklet and placing a notice on it stating that it was only available on request, Roche was in effect soliciting such requests. The Panel considered that the recipients of the booklet would understand its use; it was entitled 'Selected Abstracts on Nelfinavir' and had been available from a Roche stand, it would be viewed as promotional. The Panel did not consider that the booklet represented disguised promotion and ruled no breach of the Code in that regard. Some of the abstracts referred to the use of nelfinavir (Viracept) twice-daily which was not in accordance with its UK marketing authorization. Viracept was licensed for use three times daily in the UK. A breach of the Code was ruled.

Abbott stated that a booklet on the pharmacoenhancement of protease inhibitors was clearly displayed and freely available at the Roche stand at a BHIVA meeting. It contained several references to the off-licence use of saquinavir as once-daily and twice-daily dosing, neither of which was consistent with the product licence. Abbott alleged that the reference to off-licence use of saquinavir was inappropriate, and that prescribing information should have been included. The pre-prepared nature of this item precluded it from being categorised as being provided in response to a specific enquiry. Abbott believed that the manner in which the booklet was freely available for distribution rendered it promotional. Abbott believed it represented disguised promotion.

The Panel noted that according to the SPC the recommended dose of Fortovase for combination therapy with a nucleoside analogue was 1200mg three times daily. Details of interactions with other medicines including ritonavir related mainly to

pharmacokinetic data. The data given for the combined use of ritonavir and Fortovase related to the twice-daily use of both in healthy volunteers; it was stated that in a patient study where the two were used, doses of ritonavir greater than 400mg bd or doses of both ritonavir and saquinavir greater than 400mg bd were associated with an increase in adverse events. In the Panel's view such information did not amount to a bd dosage recommendation for Fortovase. The booklet stated that it would allow the reader to understand the principle of protease inhibitor boosting, and consider in what instances a protease inhibitor might require boosting. The booklet gave details of saquinavir (Fortovase) 400mg bd in combination with ritonavir 400mg bd. The Panel considered that requests for the booklet could not be regarded as unsolicited – by providing a copy of the booklet and placing a notice on it stating that it was only available on request, Roche was in effect soliciting such requests. The Panel considered that the booklet was promotional although this was not immediately apparent given its plain front cover. The Panel considered that the booklet was disguised promotion and a breach of the Code was ruled. The booklet referred to the use of saquinavir (Fortovase) twice-daily which was not in accordance with its UK marketing authorization. Fortovase was licensed for use three times daily. A breach of the Code was also ruled in that regard.

Upon appeal of the latter ruling by Roche, the Appeal Board noted that HIV therapy was a very specialised area; saquinavir would only be prescribed by experts. The booklet had been made available at a BHIVA meeting and was not aimed at the generality of healthcare professionals. The Panel's ruling related to the twice-daily use of saquinavir. The Fortovase SPC referred to the use of the product three times daily. The reader seeking information on special patient groups was referred to section 4.4 which included information on interaction with ritonavir. Mention was made in section 4.4 of plasma concentrations of saquinavir increasing if co-administered with ritonavir. Readers were advised to see section 4.5 'Interaction with other medicinal products and other forms of interaction' which included a sub-section headed 'Ritonavir'. This sub-section detailed the twice-daily use, in combination with ritonavir, of Fortovase. The same information was contained in the Invirase SPC. The Appeal Board thus considered that the information in the booklet with regard to the twice-daily use of saquinavir, in combination with ritonavir, was not inconsistent with the particulars listed in either the Fortovase or the Invirase SPCs. The booklet had expanded on the information given in the SPC; it had not promoted the use of saquinavir twice-daily *per se*. No breach of the Code was ruled.

Abbott stated that it had recently become aware of an incident that took place at an open forum for the public organised by NAM. The meeting was primarily organised as an information update for patients, who formed the majority of the audience. The speakers, two HIV clinicians, were asked by NAM to cover topics such as: 'How might the next

generation of anti-HIV drugs improve a patient's treatment options'; 'What are fusion inhibitors, and how will they be used?'; 'How can you get access to treatments in the clinic before they are available on prescription?'. In addition to approximately 30-35 patients in the audience, several pharmaceutical companies were represented by sales representatives, including Abbott. Abbott was not involved in any aspect of the organisation of this event, and its sales representatives did not participate in discussions arising at the meeting. Attendance by pharmaceutical representatives as such meetings was not unusual, as it allowed for a greater appreciation of patient and advocacy group issues. During the meeting questions were raised by the Roche representative when the issue of Abbott's M98-863 trial was raised. (This was one of the studies involving Abbott's developmental protease inhibitor ABT-378/r and compared ABT-378/r to nelfinavir, both arms with d4T, 3TC). The representative asked inappropriate and misleading questions of the speaker. Abbott believed that all such activities by representatives must be deemed promotional. Abbott believed that engaging in an open discussion about a company product, in a public forum attended by patients, represented direct promotion to the public. Abbott alleged that there had been unethical conduct by a representative, off-licence promotion of nelfinavir, twice-daily dosing, and promotion to the general public.

The Panel noted Roche's submission that people living with HIV were not the 'general public'. The Panel accepted that, as a group, patients with HIV/AIDS and their carers were extremely well informed about their medicines and their uses. The Panel noted, however, that any activity undertaken by a pharmaceutical company with any patient group still had to comply with the provisions of the Code. The audience was mixed; it included members of the general public and representatives from pharmaceutical companies. The Panel accepted that professionals employed in specialised therapeutic areas such as HIV/AIDS would be likely to know one another. The Roche representative was known to one of the speakers and according to the company took part in the debate on bd/tds dosing and was asked to comment on other matters during the discussion. The Panel considered that in such circumstances the representative was being asked to comment as an employee of Roche and as such must bear in mind the requirements of the Code; the representative's employer had a commercial interest in the therapeutic area. In the Panel's view it was not possible for Roche to completely dissociate itself from what the representative had said. If Roche were not responsible then the effect would be for representatives to attend and take part in patient forums as a means of the company avoiding the requirements of the Code. The Panel considered that by referring to the twice-daily dosing of nelfinavir the representative was promoting an unlicensed use of the product and a breach of the Code was ruled. Further, such comments about reduced dose frequency would be seen as beneficial and would encourage members of the general public

to ask their doctors to prescribe nelfinavir. The Panel ruled a breach of the Code in that regard also. The Panel considered that the representative had not maintained a high standard of ethical conduct and a further breach of the Code was ruled.

Abbott Laboratories Limited complained about six items produced by Roche Products Limited in relation to the HIV therapeutic area and also complained about the alleged unprofessional behaviour of a Roche representative in relation to Abbott's developmental protease inhibitor ABT-378/r (lopinavir/ritonavir).

1 Resistance workshop: special report

COMPLAINT

Abbott stated that this item was prominently displayed and freely available at the Roche stand at the HIV Pharmacy Association Meeting, September 2000, held at the Hilton National Hotel, Warwick. It was an article from the National AIDS Manual (NAM) website and fell under NAM copyright. NAM had subsequently confirmed that permission was not obtained from itself, or from the author, to use the article. The article related to comments by an HIV clinician following attendance at a Resistance and Treatment Strategies Workshop in Australia. This article comprised a subjective viewpoint of the author.

Abbott complained to Roche that this item was disparaging to ABT-378/r and Abbott. On page 1, beneath a header of 'Good to hear that they were thinking of their patients', the following statement appeared: 'The meeting was really left up on [sic] the air as to the effectiveness of ABT against virus with resistance mutations. No one really knew'. No scientific rationale was provided by the author and clearly the lasting impression for the viewer would be to cast doubt as to the effectiveness of ABT-378/r against resistant virus. Abbott believed that this statement about ABT-378/r was disparaging.

In relation to disparaging remarks about Abbott, page 1 contained the statement: '...Canadian physicians who were all saying 'buy, buy, buy' and then after the questions they were saying 'sell, sell, sell' (Clause 8.1). Once again, Abbott believed that this statement was disparaging.

In its complaint to Roche, Abbott objected to the use of this item by Roche and objected to the manner in which it was freely available on the Roche stand. Abbott claimed that the item was disparaging to Abbott and ABT-378/r. In its reply, Roche made no apology for the appearance of such an item on its promotional stand, but acceded that the item had not been certified in accordance with Clause 14 of the Code and that the item would not be used for further promotional purposes.

Abbott stated that Clause 15.2 of the Code clearly said that representatives must comply with all relevant requirements of the Code. Clause 15.10 transferred the responsibility for representative behaviour to the relevant responsible company.

Abbott was not satisfied with the response provided by Roche. Roche had not accepted that this item was disparaging to Abbott or ABT-378/r, nor appeared to appreciate the concern Abbott had as to how such an

item could appear, and be allowed to remain, on a Roche promotional stand. This item was downloaded from the Internet, displayed in a promotional manner, and was not subject to the normal process of certification for promotional material.

Furthermore, Abbott did not accept the comment by Roche that complete responsibility for this incident resided with one representative – the presence of this item on the Roche stand would have been evident to other Roche personnel present at the conference, be they other representatives at the stand, or more senior visiting personnel. All shared the responsibility to remove this item from the stand immediately.

Abbott alleged the following breaches of the Code: use of disparaging material in a promotional manner (Clause 8.1); failure of the representative to comply with the requirements of the Code (Clause 15.2); irresponsible behaviour on behalf of Roche (Clause 15.10).

RESPONSE

By way of background information, Roche explained that NAM was an independent organisation that provided scientific and medical information to people living with HIV and to the healthcare professions. Within the HIV therapeutic area no distinction was made between the nature of information required by professionals and patients. HIV community groups, advocates, scientific journalists etc and individuals living with HIV attended and actively participated at international scientific meetings. In addition, with the rapid advances made in treatments and knowledge of the disease, the Internet provided the best way of disseminating information.

However NAM was more than just an Internet site. It was an organisation with strong links to the British HIV Association (BHIVA). Details about the constitution of NAM and the services it provided and a copy of the current website home page were supplied. These details included a list of distinguished medical advisers (leading HIV physicians in the UK) who reviewed aidsmap articles. NAM also arranged regular scientific meetings and symposia. The allegation about Roche's representative [point 7 below] related to one of these meetings. NAM was an independent charity and obtained donations from many sources including the industry (Roche and Abbott).

NAM produced many publications including probably the most comprehensive manual on treatment of HIV/AIDS available in the UK. In addition its writers attended most of the major HIV conferences and wrote reports of the meetings. These reports were published in its journal and in aidsmap.com. The Resistance workshop: special report was one such report which had been produced by NAM about the International Resistance Workshop (a major scientific meeting). The report took the form of an interview between a contributing site editor based in Sydney and an HIV clinician in Australia. The item covered five key topics of interest at the meeting ie ABT-378/r, resistance testing, challenging research on drug concentrations, viral fitness and STI (structured treatment interruption). Roche did not

sponsor or have an influence on this item. Abbott claimed that it disparaged ABT-378/r. Roche disagreed for the following reasons.

In the interview the clinician was asked 'Was there new information about ABT-378?'. The reply was that there was, in patients who had already been pre-treated with antiretroviral therapy, and who could therefore be harbouring resistant strains. An accurate account was given on the type of responses seen with ABT-378/r in those patients whose virus showed various degrees of resistance. This was a balanced review of the results of the trial.

In answer to whether he thought this was a good response the clinician replied that there was a 'challenge' from the audience that patients had also been treated concurrently with efavirenz to which the patients' virus could have been sensitive. Thus efavirenz could have accounted for about 50% of the effect seen in the trial.

This description of the meeting was not a disparagement of ABT-378/r. It was based on rational scientific points debated at the meeting.

The statement about 'buy, buy, buy' and 'sell, sell, sell' was what the clinician said he heard from Canadian physicians sitting next to him at the meeting as the debate unfolded. These comments implied that if the new product [ABT-378/r] could truly overcome resistance in patients who had already failed previous protease inhibitor therapy it would be a major breakthrough (buy, buy, buy) whereas if the result was due also to another product given at the same time [efavirenz] the conclusion would be different. It was a comment that was not inappropriate to the context of the debate or to the nature of this type of interview. However the interviewer was critical of the Canadian physicians' comments as there was irony in the next point ie 'Good to hear that they were thinking of their patients'. Thus, put in context, this part of the item did not disparage Abbott, rather there was some implied criticism of the remarks from the audience.

The clinician ended by saying 'the meeting was really left up on [sic] the air as to the effectiveness of ABT against virus with resistance mutations'. Abbott stated that no scientific rationale was provided by the author for this statement but Roche disagreed. The scientific rationale was provided in the article ie that patients could have been responding to other drugs in the regimen (efavirenz and the nucleoside) and that an open label study with everyone on the same treatment had been done rather than a randomised trial. Of interest this piece was still available on the website, which suggested Abbott had not requested removal of something it considered disparaging to its product.

Roche did not believe that copyright was covered by the Code. However, on this point, Roche contacted NAM which had no objection to articles being downloaded from its site or objected to their use as long as they were not modified in any way. Roche made no modification. The piece covered important issues relating to resistance of drugs. The remainder of the article dealt with topics not involving ABT-378 and it was reproduced in full. The section on inhibitory quotient used a colloquialism (not a

quotation) to paraphrase the view of a Roche scientist who presented data at the meeting. In addition there were no claims for any Roche product.

This item was not prominently displayed at the meeting in question. About six copies had been taken to the meeting and some were provided at the stand following discussion with delegates (HIV pharmacists). However they were not on view on the stand table. Some of the copies were in a box next to the stand. The stand was left unattended at times during the meeting when it was possible that a copy was removed but they were not freely available.

In relation to the complaint, Roche submitted that the material was non-promotional (Clause 15.1), there were no claims for Roche products and it was not used in a promotional manner (Clause 8.1). It was not disparaging to Abbott or its products and it did not involve irresponsible behaviour (Clause 15.1).

PANEL RULING

The Panel noted Roche's submission that within the HIV therapeutic area no distinction was made between the nature of information required by professionals and patients. The Panel accepted that as a group, patients with HIV/AIDS and their carers were extremely well informed about their medicines and their uses. The Panel noted, however, that any activity undertaken by a pharmaceutical company in this therapeutic area still had to comply with the provisions of the Code.

The Panel noted that the Resistance workshop: special report, which referred to Abbott's product AB378, was freely available on the Internet, published by NAM, an independent organisation that provided scientific and medical information to people living with HIV and to the healthcare professions. The material appeared to be a verbatim report of an interview with an HIV physician; it was not written in scientific language and contained only the unchallenged opinion of the interviewee. Although Roche had provided donations to NAM it had not sponsored or otherwise influenced the content of the report. The report had been made available by Roche's representatives from a company stand at the HIV Pharmacy Association meeting. The Panel considered that the independent report had been used by Roche for a promotional purpose. The Panel considered that the company's use of the report in such circumstances brought it within the scope of the Code.

The Panel noted that in intercompany correspondence Roche had stated that the report was photocopied by one of its representatives; it had not been certified by the medical department. The Panel considered that the representative in question, by supplying material which had not been approved for promotional use by the company, had failed to maintain a high standard of ethical conduct and had not complied with the relevant requirements of the Code. The Panel ruled a breach of Clause 15.2. During its consideration of this matter the Panel noted that Clause 15.10 set out the responsibilities of companies for their representatives. It was not possible to breach Clause 15.10.

The Panel considered that the report disparaged Abbott and its development drug ABT-378/r as

alleged. A breach of Clause 8.1 of the Code was ruled.

2 Key Developments in Protease Inhibitors

COMPLAINT

Abbott stated that this publication was openly displayed and freely available at the Roche stand at the BHIVA meeting in October 2000. It contained a review of selected abstracts by an expert panel, and contained reference to pharmacokinetic benefits relating to twice-daily dosing of nelfinavir (Roche's product Viracept), which was contrary to the current product licence and referred to use of Abbott's currently unlicensed product ABT-378/r.

Abbott had complained to Roche about the manner in which this item was distributed, its promotional appearance, and its reference to unlicensed use of nelfinavir. Various other issues relating to data inaccuracies were also raised by Abbott.

In response, Roche denied that the item was of a promotional nature, stating that, although the item was commissioned by Roche, it was produced by a third party who 'set up an independent panel of experts to review (the) abstracts'. Roche also claimed that the item was distributed only upon request, and that the reference to off-licence use of nelfinavir was appropriate in this context. Additional responses were provided by Roche in relation to technical issues that had been raised by Abbott.

Abbott was not satisfied with the response by Roche on the key points of principle. Although Roche had stated that the item was made available only on request, this was not the case at the BHIVA meeting in question, where the item was freely on display, and freely available. Abbott believed that any item that was designed to be distributed on request only, should not by definition be freely available for the observer to read or collect.

Furthermore, Abbott believed that the fact that an 'independent panel of experts' reviewed the abstracts was irrelevant. This item was commissioned by Roche. It was freely available on display at a company stand, was of 'glossy' non-scientific appearance, and the manner in which it was distributed was promotional. As such, Abbott believed that prescribing information should have been included on the item.

Abbott did not believe that the reference to pharmacokinetic benefits of twice-daily dosing of nelfinavir, which was contrary to the current product licence, and reference to another company's unlicensed product, was acceptable for an item of a promotional nature. Furthermore, reference to the off-licence use of nelfinavir was not brought to the attention of clinicians attending this UK meeting.

Abbott believed that this item represented disguised promotion.

Abbott alleged the following breaches of the Code: disguised promotion (Clause 10.1); lack of prescribing information for a promotional item (Clause 4.1); off-licence promotion of nelfinavir (Clause 3.2); promotion of another company's unlicensed product (Clause 3.1).

RESPONSE

By way of background information, Roche explained that nelfinavir was licensed for tds dosing. The largest trial sponsored by Roche was the 542 study which compared tds versus bd dosing. This trial in addition provided the best long-term data on nelfinavir. The BHIVA guidelines stated: 'In clinical practice all of the currently available PIs (protease inhibitors), except indinavir, are taken twice-daily (bd). (Nelfinavir has not yet been licensed for bd dosing, but in practice, most patients are on bd dosing. Recent data support this schedule)'. It was within this background that Roche dealt with the question of nelfinavir posology. Roche representatives were instructed not to promote bd dosing of nelfinavir but might provide information prepared by medical information on request.

Roche stated that the Key Developments booklet, along with the items considered in points 4, 5 and 6 below, was developed as an educational piece available at the BHIVA meeting on request only. Indeed a notice was attached to the stand copy making clear that specific requests were to be made. The notice read 'Stand copy only – Please request a copy from the Roche Stand Representative'. Representatives were in constant attendance at the stand to ensure compliance with the need for requests. The exhibition area at BHIVA meetings was small compared to international meetings. International stands tended to cover large floor areas and allowed people to collect unattended items on display. In contrast, at the BHIVA meeting there was only one point where people could approach the removable items which were on a table in front of the exhibition panel.

Roche provided a sketch of its stand at BHIVA and stated that this showed that representatives could control distribution of materials at the stand. In this regard it had a completed reply paid card which it had received from Abbott (see point 3 below).

Delegates at BHIVA meetings were mostly from the UK and generally approached the stands for recent information, particularly that from major conferences they might not have attended. The Key Developments booklet was an example of such information as it was produced as an educational report on relevant abstracts from the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) which had taken place only a few weeks prior to the BHIVA meeting. It expressed the views of an independent panel.

Roche provided copies of the item in question which it believed was not promotional in nature. Each page had the same format, with the actual abstract, as printed in the conference programme, on the left side and the comments of the panel on the right side presented as bullet points. These would have incorporated comments relating to the updated results presented at the meeting. There was an introduction and a description of the panel members. All were HIV consultants of high reputation. The only briefing by Roche was with the publishers in respect of the selection of the abstracts for review.

With regard to the pharmacokinetic benefits of bd dosing of nelfinavir, and the reference to Abbott's

unlicensed medicine ABT-378/r, Roche noted that the abstract concerned was from a pivotal trial sponsored by Abbott of the boosted protease inhibitor, ABT-378/r, versus nelfinavir, a non-boosted PI. This was clearly an important study of interest to the profession. The trial randomised HIV patients naïve to treatment to either nelfinavir tds or ABT-378/r. However during the trial there was a protocol amendment allowing bd dosing of nelfinavir. The expert panel commented that this occurred because the FDA labelling changed during the study so allowing nelfinavir bd dosing in the USA. UK centres were also allowed to implement the amendment even though it was not licensed for bd dosing in Europe. The rationale for the amendment was legitimate debate. If posology did not influence adherence, it raised the question as to why the amendment was made, and the effect on outcome if bd nelfinavir had been available from the onset of the trial.

The expert panel stated that there were benefits of nelfinavir bd in terms of pharmacokinetics and exposure and BHIVA guidelines made reference to these data.

Roche disputed that this was disguised promotion and indeed that this was a promotional item. Thus there would not be the necessity for prescribing information.

On the issue of promoting another company's unlicensed product, Roche did not consider that this case was applicable to Clause 3.1. This was a balanced, scientific educational piece which discussed an important trial of Roche's product with that of a new agent. Roche did not accept that it was in breach of Clause 7.2 as the information was fair, accurate and balanced. The abstract of the data presented at the meeting was reproduced in full and the comments were independent, relevant and balanced.

Roche did not believe it was disguised promotion because Roche's involvement was acknowledged in the item, nor did it accept that it promoted off-label use of nelfinavir (Clause 3.2) when put into the context of the discussion of the trial.

PANEL RULING

The Panel noted that the Key Developments booklet was a review of selected abstracts from the 40th Interscience Conference on Microbial Agents and Chemotherapy. The abstracts, reviewed by an expert panel of four UK physicians and one from Spain, provided an overview of current thinking regarding protease inhibitors. The report stated that it had been made possible by an educational grant from Roche and had been distributed in accordance with the company's wishes. The Panel noted Roche's submission that it had briefed the publishers in respect of the selection of the abstracts for review. Three abstracts (694, 791 and 1639) referred to the twice-daily dosing of nelfinavir (Roche's product Viracept, so licensed in the USA but licensed for tds dosing in the UK) and two abstracts (424 and 693) referred to Abbott's unlicensed product ABT-378/r. The Panel noted that the booklet had been made available at the BHIVA meeting. Roche had stated that the delegates were mainly from the UK. Clause

3.1 of the Code stated that a medicine must not be promoted prior to the grant of a marketing authorization and Clause 3.2 stated that the promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in its summary of product characteristics (SPC) or data sheet. The supplementary information to Clause 3 of the Code, headed Marketing Authorization, stated that the legitimate exchange of medical and scientific information during the development of a medicine was not prohibited provided that any such information or activity did not constitute promotion which was prohibited under this or any other clause. The Panel noted that the Key Developments booklet did not meet the supplementary information to Clause 3 of the Code headed Promotion at International Conferences. The display of promotional material for medicines not licensed in the UK was permitted at international meetings held in the UK where the meeting was a truly international meeting with a significant proportion of delegates from outside the UK and promotional material for medicines or indications that did not have a UK marketing authorization must be clearly and prominently labelled as such. Material also needed to be certified as a fair and truthful presentation of the facts about the medicine. The Key Developments booklet was not labelled in accordance with the supplementary information. The Panel also queried whether the BHIVA meeting met the requirement of an international meeting with a significant proportion of delegates from outside the UK.

The Panel noted that Clause 1.2 of the Code stated that the term promotion did not include replies made in response to individual enquiries from members of the health professions but only if they related solely to the subject matter of the letter or enquiry, were accurate, did not mislead and were not promotional. This exemption to the definition of promotion did not apply as the requests were not unsolicited and the Panel had decided that the booklet was promotional.

The Panel noted that the Key Developments booklet had been sponsored by Roche. The content of the booklet would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose. Even if neither of these applied, the company would be liable if it had been able to influence the content of the booklet in a manner favourable to its own interests. It was possible for a company to sponsor material which mentioned its own products and not be liable under the Code for its content, but only if it had been a strictly arm's length arrangement with no input by the company and no use made by the company of the material for promotional purposes.

The Panel considered that the Key Developments booklet was a promotional item. The A4 booklet had a glossy, colourful front cover. Roche had briefed the publisher with regard to the selection of the abstracts – there were 15 and all but one of them mentioned Roche's products nelfinavir or saquinavir (Fortovase) in the abstract or its associated comments. The booklet had been on the company's stand at the BHIVA meeting.

The Panel noted Roche's submission that the booklet was available on request only and that a copy on the stand made this clear. Copies of labels provided by Roche read 'Stand copy only – please request a copy from the Roche Stand Representative'. The Panel considered that such requests for the booklet could not be regarded as unsolicited, by providing a copy of the booklet and placing such a notice on it Roche was in effect soliciting such requests.

The Panel noted that the booklet was subtitled 'A review of selected abstracts by an expert panel'. The Panel considered that some readers might assume that the abstracts had been chosen by the expert panel whereas in fact they had been chosen by Roche and for the most part mentioned its products. The Panel did not consider that readers had been provided with sufficient explanations about the company's role in the selection of the abstracts. The Panel considered that the booklet was in fact disguised promotion and a breach of Clause 10.1 was ruled.

The abstracts referred to Roche's products but the booklet did not contain the prescribing information for them. The Panel ruled a breach of Clause 4.1 of the Code.

Some of the abstracts referred to the use of nelfinavir (Viracept) twice-daily which was not in accordance with its UK marketing authorization. Viracept was licensed for use three times daily in the UK. A breach of Clause 3.2 was ruled.

The Panel noted that although the booklet referred to Abbott's unlicensed product ABT-378/r, Roche was not promoting Abbott's product and therefore the Panel considered that Clause 3 did not apply and no breach was ruled in this regard. The Panel queried whether the reference to Abbott's unlicensed medicine met the requirements of Clause 7.2 of the Code. There was no mention that the product was unlicensed. Abbott could not counter the arguments as it would be open to accusations of promoting an unlicensed medicine. The Panel noted that there was no complaint regarding Clause 7.2.

3 Reply paid card

COMPLAINT

Abbott stated that this item was prominently displayed and freely available on the Roche stand at a BHIVA meeting in March 2000. It was designed to record physician interest in company products and the enquiry was subsequently passed to the medical department for further action.

Abbott complained to Roche that this item contained reference to off-licence use of both nelfinavir and saquinavir and that it was clearly inviting the enquirer to request information that fell beyond the current marketing authorizations for both products.

Roche replied by stating that the item was not used in a promotional manner, no claims were made about the products, and that the card reflected common questions posed to the drug information department.

Abbott accepted that requests for information relating to off-licence use of products should be directed to the medical department of the relevant company, and that

many companies used reply paid cards of this nature. However, this item did not allow for the registration of an enquiry about a product, merely that further information was required. In the absence of a specific medical enquiry, Abbott believed that it was inappropriate to have pre-printed cards freely available on a promotional stand that invited enquiries about the unlicensed use of a product. Abbott believed that this would result in the company supplying information that it felt the enquirer would want, as the card did not allow for any enquiry other than those the company had detailed on the card. Abbott believed that use of cards in this manner was a practice that effectively solicited for information requests.

Abbott alleged the following breaches of the Code: that use of this card in this manner represented disguised promotion (Clause 10.1) and promotion beyond the scope of the product licence (Clause 3.2).

RESPONSE

Roche confirmed that the reply paid card had been available at the BHIVA meeting in March 2000. It had been updated since and the updated version was also used at the BHIVA meeting in October. Roche provided a copy of the latest version.

Roche submitted that the reply paid card reflected commonly requested information. It allowed the requester to tick a box for a specific piece of information. There was no soliciting for a request. In addition three of the four topics on the reply paid card were not inconsistent with the SPCs for the products (Clause 3.2). This was not an item for disguised promotion. The relevant information was in some cases provided at the meeting and the reply paid cards were marked accordingly at the time or when returned to head office to avoid duplication by medical information.

The original reply paid card listed four topics.

- Nelfinavir was indicated in patients with high viral loads. There was no distinction made in terms of viral load in the SPC.
- Twice-daily nelfinavir was outside of the current licence but Roche was frequently asked for information on this and it was recommended in the BHIVA guidelines.
- The third and fourth topics listed were for information on saquinavir when used in combination with ritonavir. As per Clause 3.2 this was information not inconsistent with the particulars listed in the SPC for Fortovase.

Roche did not accept that having this available on the stand at the BHIVA meeting constituted promotion. There were no claims on the card. Roche did not consider this to be a covert way of providing unsolicited information. Clause 1.2 (supplementary information) provided for materials to be prepared for common enquiries as long as they appeared non-promotional.

Thus Roche maintained that the use of this card did not represent disguised promotion (Clause 10.1) nor promotion beyond the scope of the product licence (Clause 3.2).

PANEL RULING

The Panel noted that the copy of the reply paid card, as provided by Abbott, allowed the person filling it in to request information on four topics; nelfinavir in high viral loads; twice-daily nelfinavir; saquinavir with mini-dose ritonavir and once-daily saquinavir soft capsule. The Panel noted that, according to the relevant SPCs, Viracept (nelfinavir) and Fortovase (saquinavir) were both only licensed for use three times daily. The Panel accepted that some people would be interested in alternative dosing schedules for each product but considered that by referring to such uses on a reply paid card Roche was soliciting enquiries and in effect promoting use of the products in a way which was inconsistent with the particulars listed in their respective SPCs. A breach of Clause 3.2 was ruled.

The Panel considered that recipients of the reply paid card would understand its use; such items were often used by the industry in association with promotion. The Panel did not consider that the reply paid card represented disguised promotion and ruled no breach of Clause 10.1 of the Code.

4 Post Conference Scientific Slide Service

COMPLAINT

Abbott stated that this item was also prominently displayed and freely available on the Roche stand at the BHIVA meeting in March 2000. It was a pre-prepared collection of slides relating to various clinical trials involving Roche's products, including nelfinavir at a twice-daily dose (slide 3) which was not consistent with the current product licence.

Abbott complained to Roche that there were references to an unlicensed use of nelfinavir within this item, and that the manner in which this item was available rendered the item promotional. As such, Abbott claimed that the reference to off-licence use of nelfinavir was inappropriate, and that this piece should have included prescribing information.

In response, Roche claimed that the item was non-promotional, and that it was designed to be supplied following a specific request only.

Abbott accepted that the overall appearance of this item was non-promotional, and that the legitimate exchange of scientific information at a scientific conference was permitted by the Code. However, Abbott believed that the provision of scientific information relating to off-licence use of a product must be handled by the medical department, and that the response must be tailored to the relevant enquiry. Production of a slide set that referred to off-licence use of a product presumed to predict the nature of the enquiry. As such, the enquirer received what the company felt he/she should receive about its product, and not what he/she actually requested.

The item was freely available on the Roche stand. The enquirer could either remove the whole item from the stand for reference, or request a selection of slides subsequently. In either case information relating to an unlicensed use of a product would be supplied without a specific enquiry, and the provision of information could not be tailored to the nature of the enquiry.

Abbott alleged the following breaches of the Code: disguised promotion (Clause 10.1); promotion of nelfinavir (as a bd dose), which was inconsistent with the current product licence (Clause 3.2).

RESPONSE

Roche noted that Abbott accepted that this was not a promotional item and that the legitimate exchange of scientific information at a scientific conference was permitted by the Code.

The item was designed as a small catalogue of slides, from which the reader could order an individualised set. The majority of slides were from presentations given at international conferences. The first set related to nelfinavir in high viral loads. This was consistent with the licence. The second set was the result of study 542, the pivotal study of nelfinavir mentioned above. The next set of slides related to resistance and sequencing which was entirely within the current SPC for nelfinavir. The next set related to a comparison of virological response to different protease inhibitors and nevirapine (all licensed in the UK) from the largest cohort of patients in the UK. All information provided was consistent with current licences and no mention was made of nelfinavir posology. There were two slides that compared results across trials for different protease inhibitors, again entirely consistent with all the licences. The Cheese study was a trial of Fortovase versus indinavir both at licensed doses. Finally there was a set of slides relating to the pivotal registration trial (NV15355) of Fortovase versus Invirase at standard licensed doses of each product.

Representatives were not provided with this item. The labelling of the stand copy was provided. The slide or slides themselves were only available on request and thus the item was tailored to a specific request.

Roche therefore submitted that there had not been a breach of the Code. The item was not disguised promotion (Clause 10.1) nor did it promote nelfinavir as bd (Clause 3.2).

PANEL RULING

The Panel noted that the catalogue, entitled 'Post-Conference Scientific Slide Service', contained pictures of 78 slides which detailed a number of separate studies all of which had involved the use of Roche's products nelfinavir or saquinavir. One of the studies (study 542) reported the use of twice-daily nelfinavir and the conclusion slide for that study stated that '... BID nelfinavir is equally effective to TID nelfinavir during 96 weeks of therapy'. A statement on the front cover read 'To order an individualised slide set on PowerPoint format, select required slides from this catalogue and complete the accompanying request form'. It was stated that the service was provided by the Drug Information Department. The Roche logo was on the back cover.

The Panel noted that the legitimate exchange of medical and scientific information during the development of a medicine was not prohibited provided that any such information or activity did not

constitution promotion prohibited by Clause 3 of the Code or any other clause.

The Panel considered that the slide catalogue was a promotional item. All of the studies detailed in the slide sets had involved the use of one of Roche's products and the catalogue had been made available on the company's stand at a BHIVA meeting. The Panel noted that the catalogue was entitled 'Post Conference Scientific Slide Service'. The Panel considered that some readers might assume that it contained details of slides of all the presentations at a conference whereas in fact each study included involved one of Roche's products. The Panel noted that the catalogue and the individual slides were available on request only but considered that such requests were not unsolicited; Roche's provision of the catalogue on its stand was in effect soliciting such requests.

The Panel considered that the catalogue amounted to disguised promotion and a breach of Clause 10.1 was ruled. Some of the slides referred to the use of nelfinavir (Viracept) twice-daily which was not in accordance with its UK marketing authorization. Viracept was licensed for use three times daily in the UK. A breach of Clause 3.2 of the Code was ruled.

During its consideration of this matter the Panel noted its ruling of a breach of Clause 4.1 in point 2 above and although it made no ruling in this regard as no allegation had been made it considered that the catalogue should similarly have included prescribing information for the Roche products mentioned.

5 Selected Abstracts on Nelfinavir

COMPLAINT

Abbott stated that this item was prominently displayed and freely available on the Roche stand at the BHIVA meeting in March 2000. It contained numerous abstracts pertaining to nelfinavir, both in currently licensed (tds) and unlicensed (bd) dosing frequencies. The attention of the viewer was not drawn to the currently unlicensed status of bd nelfinavir and this item was without reference to prescribing information.

Abbott complained to Roche that there were references to an unlicensed use of nelfinavir within this item, and that the manner in which this item was available rendered it promotional. As such, Abbott claimed that the reference to off-licence use of nelfinavir was inappropriate, and that this piece should have included prescribing information.

In response, Roche claimed that the item was non-promotional, and that it was, as with the slide catalogue [point 4 above], designed to be supplied following a specific request only. Abbott stated that its comments made about the slide catalogue above applied to this item too.

As this item was freely available on display at a scientific meeting, contained reference to an unlicensed dosage form for nelfinavir, and was designed to provide information that could not be tailored to the nature of an enquiry, Abbott believed this item was used in a promotional manner.

Abbott considered that the provision of scientific information relating to off-licence use of a product must be handled by the medical department, and that the response must be tailored to the relevant enquiry. Production of a collection of abstracts that referred to off-licence use of a product presumed to predict the nature of the enquiry. As such, the enquirer received what the company felt he/she should receive about its product, and not what he/she actually requested.

Abbott alleged the following breaches of the Code: disguised promotion (Clause 10.1); promotion of nelfinavir (as a bd dose), which was inconsistent with the current product licence for nelfinavir (Clause 3.2).

RESPONSE

Roche stated that this item was available at the BHIVA meeting in March 2000 but under the same conditions as specified in point 2 above for the October meeting.

Roche considered this item to be educational and not promotional. It was made available on request according to the terms outlined above.

The abstracts were presented as follows:

Efficacy

- AG1343-511. This was the pivotal phase III trial used to obtain the licence for nelfinavir. It compared two doses of nelfinavir given tds. Thus all the information provided was consistent with the SPC.
- AG1343-542. This was the pivotal trial of nelfinavir tds versus bd, which had been presented at several scientific meetings and also provided the best information on long-term dosing of nelfinavir. Data from this trial on long-term use of tds and bd dosing superseded that in 511 above because it was larger and contained more data on the standard dose of 750mg tds. It had a longer follow up than study 511 for both tds and bd dosing. Thus the study results were not just relevant to bd dosing. This was made clear in the conclusion of the abstract. The results were not presented in an unbalanced or promotional manner and there was a statement to the effect that bd dosing was not a licensed dosing regimen in the UK.
- AG1343-509. This showed results of nelfinavir given tds. Thus it was entirely consistent with the licence. There were no claims made inconsistent with the licence.

Implications for future treatment

- Cohen *et al* (2000). This was an abstract on phenotypic resistance testing which was of great recent relevance. It showed that resistance testing improved outcome. This trial did not directly involve any of Roche's products and no claims relating to Roche's products were made, which further illustrated the fact that this whole item was designed as an educational service for the profession and not as a promotional piece.
- Haubrich *et al* (1999). This was a piece on resistance testing and its value in determining the

sequencing of antiretroviral drugs. It showed that patients who started on indinavir and became resistant would most likely be cross-resistant to nelfinavir whereas patients starting on nelfinavir who became resistant might be salvaged by indinavir. This was an important finding, which was of great relevance to sequencing of treatments. It contained no mention whatsoever of dosing posology. It was entirely consistent with the licence. Roche used this to advise physicians where nelfinavir should be used and in what sequence.

- Tebas *et al* (1999). This abstract complemented Haubrich as it showed that when patients failed on nelfinavir the unique pattern of resistance meant those patients could be salvaged with a combination of saquinavir and ritonavir. The dosage of nelfinavir used in this study was tds. Indeed these patients were from the AG1343-511 study referred to above thus showing how this item linked various elements of recent research data together in a comprehensive way. The dosage of saquinavir and ritonavir was 400/400mg. There was a wealth of data on the efficacy of this regimen and reference to the SPC showed that the dosage regimen was not inconsistent with the licence (see also point 6 below).
- Tebas *et al* (1999). This was the follow up study of the Tebas data above. Again all the data, results and conclusions were accurate, balanced and consistent with the licences of Roche antiretrovirals.
- Zolopa *et al* (1999). These were data presented at ICAAC, a major international meeting. There were no claims for any off label use of Roche products.
- Deeks *et al* (1998). This was a piece relating to the use of saquinavir/ritonavir in patients who had failed an indinavir or ritonavir containing regimen. Again there were no claims made inconsistent with the licence.

Thus this item was consistent with an educational approach. Of the nine abstracts selected for inclusion in this item, one made reference to bd dosing of nelfinavir and this was put into the appropriate context, and included the statement on the licence status of bd in the UK. All of the other abstracts were inter-related within the theme of sequencing of antiretroviral treatment.

It was a balanced scientific abstract book. Roche believed that as such the point about being tailored to the nature of the enquiry was irrelevant to this particular item. The bulk of it related to licensed use of Roche's products. Roche did not accept that it was disguised promotion (Clause 10.1) nor promotion of nelfinavir in a way inconsistent with the SPC nor that it promoted bd dosing (Clause 3.2).

PANEL RULING

The Panel noted that the booklet entitled 'Selected Abstracts on Nelfinavir' contained a number of abstracts detailing the efficacy of nelfinavir and

discussing the implications for future treatment. Some of the abstracts referred to saquinavir (Fortovase). Use was made, within the abstracts, of boxed text to highlight important points. The conclusion 'box' of an abstract detailing the results of a trial which had compared the use of nelfinavir bd and tds stated that both dosing schedules were equally effective during 96 weeks of therapy and that both showed a consistent, long-term improvement in cell count.

The Panel noted its comments made in paragraphs 2, 3 and 4 of its ruling in point 2 above and considered that they also applied here.

The Panel considered that the abstracts booklet was a promotional item, it was not an educational piece as submitted by Roche. The subject of the booklet was nelfinavir, Roche's product Viracept. The booklet had been on the company's stand at a BHIVA meeting. The Panel noted Roche's submission that the booklet was made available only on request and understood that to mean that a copy on the stand was labelled 'Stand copy only – Please request a copy from the Roche Stand Representative'. The Panel considered that such requests for the booklet could not be regarded as unsolicited – by providing a copy of the booklet and placing a notice on it stating that it was only available on request, Roche was in effect soliciting such requests.

The Panel considered that the recipients of the booklet would understand its use; it was entitled 'Selected Abstracts on Nelfinavir' and had been available from a Roche stand, it would be viewed as promotional. The Panel did not consider that the booklet represented disguised promotion and ruled no breach of Clause 10.1 of the Code. Some of the abstracts referred to the use of nelfinavir (Viracept) twice-daily which was not in accordance with its UK marketing authorization. Viracept was licensed for use three times daily in the UK. A breach of Clause 3.2 was ruled.

During its consideration of this matter the Panel noted its ruling of a breach of Clause 4.1 in point 2 above and although it made no ruling in this regard as no allegation had been made it considered that the abstract booklet should similarly have included prescribing information for the Roche's products mentioned.

6 Pharmacoenhancement of Protease Inhibitors COMPLAINT

Abbott stated that this booklet was clearly displayed and freely available at the Roche stand at the BHIVA meeting in October 2000. It contained several references to the off-licence use of saquinavir as once-daily, and twice-daily dosing, neither of which were consistent with the current product licence. No prescribing information was included in the publication. The booklet was designed to provide clinicians with information relating to pharmacoenhancement between protease inhibitors.

Abbott complained to Roche that there were references to an unlicensed use of saquinavir and that the manner in which the booklet was available

rendered it promotional. As such, Abbott claimed that the reference to off-licence use of saquinavir was inappropriate, and that this piece should have included prescribing information.

In response, Roche claimed that the booklet was non-promotional, and that it was, as with the material considered in points 4 and 5 above, designed to be supplied following a specific request only. Abbott stated that its comments at points 4 and 5 applied.

Abbott accepted that the issue of pharmacoenhancement with protease inhibitors was currently extremely topical, and a source of great debate. However, the booklet was freely available on the Roche promotional stand at a meeting attended by mainly UK physicians. It clearly contained information relating to off-licence use of saquinavir, with no attempt having been made to draw the attention of the viewer to this. The pre-prepared nature of this item precluded it from being categorised as one providing information provided in response to a specific enquiry.

Abbott believed that the manner in which the booklet was freely available for distribution rendered it of a promotional nature. As such, it should have contained prescribing information and should not have made references to the unlicensed dosage of a Roche product. Abbott believed this represented disguised promotion.

Abbott alleged the following breaches of the Code: disguised promotion (Clause 10.1); promotion of saquinavir (as a once and twice-daily dose), which was inconsistent with the current product licence for saquinavir (Clause 3.2)

RESPONSE

Roche stated that its comments about the free availability of items at the BHIVA meeting in October 2000 [made in point 2 above] applied to this booklet.

The booklet was educational rather than promotional. Representatives did not use it to promote. It was available normally from Roche's medical information department on request. It was available at BHIVA on request. The labelling was provided. It included a section on the current pharmacoenhanced protease inhibitors.

The section on saquinavir in combination with ritonavir started with two important and relevant statements

- Saquinavir had demonstrated clinical efficacy as a sole protease inhibitor in antiretroviral combination therapy.
- Saquinavir was licensed to be taken three times daily with food. To reduce this dosing frequency and the number of capsules required studies had investigated the use of saquinavir in combination with ritonavir.

Thus at the outset the booklet had specified the clinical efficacy of saquinavir without pharmacoenhancement and the current licensed dosing of saquinavir as a single unboosted protease inhibitor.

The section continued by explaining the work that had been done in combination with ritonavir. The SPC of Fortovase included information on such concurrent use. Thus under section 4.5 (Interaction studies performed with Fortovase) subsection 'ritonavir' details were given of combinations of bd dosing of different combinations of saquinavir either as Fortovase or Invirase (hard capsules) and ritonavir in patients and volunteers. Thus the information given in this booklet on the boosting of saquinavir with ritonavir was not inconsistent with the SPC (Clause 3.2). In addition the data on once-daily dosing was clearly shown to be in volunteers only.

In addition the booklet was balanced in its discussion of the side effects of pharmacoenhancement. The risks of this strategy were clearly outlined (page 10 of the booklet) including the lack of clinical data. Indeed it specifically stated that there was a lack of large, long-term trials except for saquinavir 400mg plus ritonavir 400mg. The other risks such as increased side effects, possible increase in metabolic disorders, additive side effects and drug interactions were included, as was the impact on cost.

In addition there was a recommendation to carry out therapeutic drug monitoring among other things to limit toxicity.

In summary this was an educational piece which was balanced and fair. The data presented on saquinavir and ritonavir was consistent with the SPC for Fortovase and it was not therefore a disguised promotional piece (Clause 10.1).

PANEL RULING

The Panel noted that according to the SPC the recommended dose of Fortovase, for combination therapy with a nucleoside analogue, was 1200mg three times daily. Section 4.5 of the SPC gave details of interactions with other medicines including ritonavir; these details related mainly to pharmacokinetic data. The data given for the combined use of ritonavir and Fortovase related to the twice-daily use of both in healthy volunteers; it was stated that in a patient study where the two were used doses of ritonavir greater than 400mg bd or doses of both ritonavir and saquinavir greater than 400mg bd were associated with an increase in adverse events. In the Panel's view such information did not amount to a bd dosage recommendation for Fortovase.

The Panel noted that the booklet entitled 'Pharmacoenhancement of Protease Inhibitors' was subtitled 'A review of recent presentations'. The front cover was just black and white. Inside it was stated that the booklet would allow the reader to understand the principle of protease inhibitor boosting, and consider in what instances a protease inhibitor might require boosting. The booklet gave details of saquinavir (Fortovase) 400mg bd in combination with ritonavir 400mg bd.

The Panel noted its comments made in paragraphs 2, 3 and 4 of its ruling in point 2 above and considered that they also applied here.

The Panel considered that the booklet was a promotional item, it was not an educational piece as

submitted by Roche. The booklet had been produced by Roche and discussed the use of one of its products. The booklet had been made available from a company stand. The Panel understood that the copy of the booklet on the stand was labelled 'Stand copy only – Please request a copy from the Roche Stand Representative'. The Panel considered that such requests for the booklet could not be regarded as unsolicited – by providing a copy of the booklet and placing a notice on it stating that it was only available on request, Roche was in effect soliciting such requests.

The Panel considered that the booklet was promotional although this was not immediately apparent given its plain front cover. The Panel considered that the booklet was thus disguised promotion and a breach of Clause 10.1 was ruled. The booklet referred to the use of saquinavir (Fortovase) twice-daily which was not in accordance with its UK marketing authorization. Fortovase was licensed for use three times daily. A breach of Clause 3.2 was ruled.

During its consideration of this matter the Panel noted its ruling of a breach of Clause 4.1 in point 2 above and although it made no ruling in this regard as no allegation had been made it considered that the booklet should similarly have included prescribing information for the Roche products mentioned.

APPEAL BY ROCHE

Roche appealed the ruling of a breach of Clause 3.2.

Roche noted that Clause 3.2 stated that the promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in its SPC or data sheet.

The indication for Fortovase (saquinavir soft capsules) was in combination with antiretroviral agents for the treatment of HIV-1 infected adult patients.

Roche noted that ritonavir was an antiretroviral agent, thus Fortovase was indicated for use in combination with ritonavir.

Roche also noted that details concerning the concurrent use of Fortovase with ritonavir were provided in the SPC for Fortovase under Section 4.5 which included details of combinations of saquinavir and ritonavir given as bd dosing in both volunteers and patients. In addition the SPC described warnings relating to the combined use. Similar details were provided in the SPC of Invirase (saquinavir hard capsules).

Roche stated that the information provided by the SPCs should be viewed within the context of the standard of care for HIV infected persons. This was outlined in the guidelines of the British HIV Association.

Roche stated that protease inhibitors were potent antiretrovirals, which had improved the treatment of HIV when used in triple or quadruple antiretroviral drug combinations. However all protease inhibitors exhibited highly variable inter-patient bioavailability and pharmacokinetics. This had led to the routine use

of most protease inhibitors (saquinavir, indinavir and amprenavir) in combination with a medicine or medicines (usually ritonavir) which enhanced the bioavailability by inhibiting metabolism of the parent protease inhibitor. There was a section within the British HIV Association guidelines which recommended such a regimen. Physicians wishing to prescribe a combination of saquinavir either as Fortovase or Invirase could find adequate details of such a combination together with the warnings and precautions within the SPC.

Roche noted that a recent change to the Invirase SPC included a statement that Invirase might only be given in combination with other antiretroviral agents (such as ritonavir) which increased its bioavailability.

Therefore Roche submitted that the information provided in the pharmacoenhancement booklet in relation to saquinavir was in accordance with the terms of the marketing authorization and was not inconsistent with the particulars listed in the SPCs of both Fortovase and Invirase and therefore did not constitute a breach of Clause 3.2.

APPEAL BOARD RULING

The Appeal Board noted that HIV therapy was a very specialised area; saquinavir would only be prescribed by experts. The Pharmacoenhancement booklet had been made available at the BHIVA meeting and was not aimed at the generality of healthcare professionals. The Panel's ruling related to the twice-daily use of saquinavir.

The Appeal Board noted that section 4.2 of the Fortovase SPC, 'Posology and method of administration', referred to the use of the product three times daily. From section 4.2 the reader seeking information on special patient groups was referred to section 4.4 which included information on interaction with ritonavir. Mention was made in section 4.4 of plasma concentrations of saquinavir increasing if co-administered with ritonavir. Readers were advised to see section 4.5 'Interaction with other medicinal products and other forms of interaction' which included a sub-section headed 'Ritonavir'. This sub-section detailed the twice-daily use, in combination with ritonavir, of Fortovase. The same information was contained in the Invirase SPC.

The Appeal Board thus considered that the information in the booklet with regard to the twice-daily use of saquinavir, in combination with ritonavir, was not inconsistent with the particulars listed in either the Fortovase or the Invirase SPCs. The booklet had expanded on the information given in the SPC; it had not promoted the use of saquinavir twice-daily *per se*. No breach of Clause 3.2 was ruled. The appeal was successful.

7 Inappropriate representative behaviour

COMPLAINT

Abbott stated it had recently become aware of an incident that took place at an open forum for the public organised by a leading advocacy group (NAM) in September 2000. The meeting was primarily organised as an information update for patients, who

formed the majority of the audience. The speakers, two HIV clinicians from centres in London, were asked by NAM to cover topics such as: 'How might the next generation of anti-HIV drugs improve a patient's treatment options?'; 'What are fusion inhibitors, and how will they be used?'; 'How can you get access to treatments in the clinic before they are available on prescription?'

In addition to approximately 30-35 patients in the audience, several pharmaceutical companies were represented by sales representatives, including Abbott. Abbott was not involved in any aspect of the organisation of this event, and its sales representatives did not participate in discussions arising at the meeting. Attendance by pharmaceutical representatives at such meetings was not unusual, as it allowed for a greater appreciation of patient and advocacy group issues in this therapeutic area.

During the meeting questions were raised by the Roche representative when the issue of Abbott's M98-863 trial was raised. (This was one of the studies involving Abbott's developmental protease inhibitor ABT-378/r and compared ABT-378/r to nelfinavir, both arms with d4T, 3TC). The representative asked inappropriate and misleading questions of the speaker as follows:

- 1 '...if he knew whether the difference at 24 weeks between ABT-378/r and nelfinavir was significant'.
- 2 With reference to the M98-836 trial protocol, the representative stated that:
 - a) At ICAAC, Novak and Munsiff had proven that nelfinavir bd was more efficacious than tds dosing and that Roche was filing for bd licensing.
 - b) The trial was a randomised, double-blind study, so the lunch time dose of active nelfinavir would be detrimental to the nelfinavir results but not ABT-378/r. The speaker pointed out that the protocol was written 3 years ago and nelfinavir was licensed at a tds dose.
- 3 The representative asked one of the speakers if he knew of any information on how to salvage ABT-378/r failures. He said he had no knowledge.
- 4 The representative questioned one of the speakers if he was aware of the resistance profile or mutations associated with ABT-378/r. Another speaker replied that there were no primary mutations known.

In its complaint to Roche, Abbott stated that the behaviour of the representative was wholly inappropriate, and was of particular concern as this was a meeting attended in the main by patients. Abbott claimed that it was inappropriate to discuss another company's unlicensed product in a public forum, and in an unsolicited manner. Furthermore, Abbott objected to the clear reference to an unlicensed dosing regimen for a Roche product, made by a Roche representative, at such an event. Abbott claimed that this represented promotion to the general public, and conduct unbecoming to a sales representative.

In response, Roche stated that the representative in question was highly qualified, and that questions such as had been raised were acceptable in 'high calibre scientific meetings'. Roche accepted that the venue

was not an appropriate one 'to raise these matters especially if the presenter was not completely involved in the study'. In Abbott's opinion, this latter comment was entirely irrelevant. Either a sales representative was permitted by the Code to discuss off-licence use of products in a public meeting, or not.

The response provided by Roche was wholly unacceptable to Abbott. Abbott believed that a sales representative, regardless of scientific background, was considered by those outside a company to have a primary motive for promoting the sale of medicines. As such, Abbott believed that all such activities by representatives must be deemed promotional. Furthermore, Abbott believed that engaging in an open discussion about a company product, in a public forum attended by patients, represented direct promotion to the public.

Abbott was concerned that this critical issue had not been accepted by Roche. There was a vast difference in permitting members of the scientific department to comment/present at a scientific venue, compared to a sales representative openly discussing unlicensed products, and the off-licence use of licensed products, at a patient forum.

Abbott alleged the following breaches of the Code: unethical conduct by a representative (Clause 15.2); off-licence promotion of nelfinavir, twice-daily dosing (Clause 3.2); promotion to the general public (Clause 20).

Abbott was concerned that two issues, this matter and the one considered in point 1 above, related to inappropriate representative behaviour. This would imply that procedures aimed at ensuring representative compliance with the Code were lacking. Roche had failed to reassure Abbott that this was not the case.

RESPONSE

Roche referred to the nature of NAM and its educational meetings provided in the background information to point 1 above. NAM was more than a 'leading advocacy group'.

Roche submitted that this was a scientific meeting open to people living with HIV but also to members of the profession and to the industry. Representatives of many companies including Abbott and Roche attended the meeting. The NAM poster outlining topics at this meeting was provided. This showed that data on two new protease inhibitors were to be presented. One of these was the Abbott product ABT-378/r. The speakers were a consultant physician and a hospital pharmacist. The hospital pharmacist included the results of the ABT-378/r versus nelfinavir study (referred to frequently above) in his presentation.

The representative from Roche was a PhD molecular biologist who originally worked within the company's HIV diagnostics division but had recently transferred to pharmaceutical sales.

Roche did not instruct the representative to attend this meeting; like many of its employees there was individual commitment to this disease area and attendance at this evening meeting was in the

representative's own time. However Roche also considered this to be a scientific meeting and not one subject to the Code and thus questions raised in the meeting would be in that context.

Following the presentation of the data, Roche's representative took part in the debate. The consultant physician made reference to tds/bd dosing in the trial in relation to the results. Roche's representative as part of this discussion stated that there was data on bd and that this dosing schedule was licensed in the USA but not in the UK. Roche did not accept that this was promotional or that the other questions raised by the representative were inappropriate within the context of the meeting. The consultant physician knew the representative, knew that the representative was employed by Roche and indeed had asked the representative to comment on other matters during the discussion.

Abbott's complaint related to a representative promoting 'at an open forum for the public'. Roche submitted that people living with HIV were not the 'general public'. Their knowledge and demands for information about current and future treatments were such that companies involved in research had come to take an open approach. It was not the case as Abbott stated that all activities of representatives must be deemed promotional. There were situations where this was not the case eg provision of information in response to individual enquirers (Clause 1.2) and reporting of ADRs (Clause 15.6).

The representative did not spontaneously volunteer information on nelfinavir or ask questions which were not related to the presentations. The questions and statements made should be taken in context. They related to dosing of a licensed product (nelfinavir) in the context of a trial comparing it to an unlicensed product. If Abbott believed that this was an open public forum then it endorsed the dissemination of information on an unlicensed product by the presence of its representatives at the meeting, particularly as one of the topics was access to treatments not available on prescription.

Roche representatives were trained on the Code. Roche did not specifically brief representatives about raising questions or making comments at scientific meetings which were not organised by the company and which the representative was attending voluntarily, as in this case. Roche did not instruct representatives to attend or not to attend such meetings. However the company did not discourage attendance.

In summary Roche did not believe that this was unethical conduct (Clause 15.2) or off-licence

promotion of nelfinavir (Clause 3.2) or promotion to the general public (Clause 20).

PANEL RULING

The Panel noted Roche's submission that people living with HIV were not the 'general public'. The Panel accepted that as a group, patients with HIV/AIDS and their carers were extremely well informed about their medicines and their uses. The Panel noted, however, that any activity undertaken by a pharmaceutical company with any patient group still had to comply with the provisions of the Code.

The Panel noted that the representative had both a current commercial and a past intellectual interest in the meeting having previously worked as a molecular biologist in Roche's HIV diagnostics division. The meeting was open to anyone who would like to attend and so the audience was mixed; it included members of the general public and representatives from pharmaceutical companies. The Panel accepted that professionals employed in specialised therapeutic areas such as HIV/AIDS would be likely to know one another. The Roche representative was known to one of the speakers and according to the company took part in the debate on bd/tds dosing and was asked to comment on other matters during the discussion. The Panel considered that in such circumstances the representative was being asked to comment as an employee of Roche and as such must bear in mind the requirements of the Code; the representative's employer had a commercial interest in the therapeutic area. In the Panel's view it was not possible for Roche to completely dissociate itself from what the representative had said. If Roche were not responsible then the effect would be for representatives to attend and take part in patient forums as a means of the company avoiding the requirements of the Code.

The Panel considered that by referring to the twice-daily dosing of nelfinavir the representative was promoting an unlicensed use of the product in breach of Clause 3.2 of the Code. A breach of that clause was ruled. Further, such comments about reduced dose frequency would be seen as beneficial and would encourage members of the general public to ask their doctors to prescribe nelfinavir. The Panel ruled a breach of Clause 20.2. The Panel considered that the representative had not maintained a high standard of ethical conduct and a breach of Clause 15.2 was ruled.

Complaint received **10 November 2000**

Case completed **9 April 2001**

HOSPITAL PHARMACIST v SCHERING-PLOUGH

Clarityn and Nasonex promotional item

A hospital pharmacist complained about a four page document entitled 'The treatment of allergic conditions' which had been issued by Schering-Plough. It was subtitled 'The use of Clarityn and Nasonex in patients with seasonal allergic rhinitis and perennial rhinitis, and Clarityn in urticaria'.

The complainant believed that the document provided doctors and pharmacists with misleading and incorrect information. The complainant, who had been preparing an evaluation on nasal corticosteroid sprays, in particular Nasonex versus Flixonase, noted that a table comparing the cost of the sprays and the number of metered doses per unit, leading to a comparative cost per day, stated that fluticasone propionate (A&H) contained 120 metered doses whereas in reality it was available [at the same price] as a 150 metered dose size. This made fluticasone 30p per day rather than 38p and therefore the cheaper product. In all other respects the complainant could see no real difference between the products.

The Panel noted that Schering-Plough had submitted that the document had been withdrawn and revised in February 2000 as soon as it was made aware of the addition of a fluticasone 150 unit pack. The complainant had used the document for an evaluation well after April and maintained that out-of-date information had been supplied. The complainant was nonetheless pleased that Schering-Plough had amended the document.

The Panel noted that it was difficult to progress the matter any further as the complainant was not willing to be identified to Schering-Plough. The company could not investigate the matter further as it could not identify who had given the document to the complainant. It was difficult to establish exactly what had happened. Schering-Plough had updated the document once the presentation of fluticasone had changed. Representatives had been instructed to withdraw the document and a replacement had been issued. A factor that might have contributed to the situation was that neither document bore a date of preparation as required by the Code. The Panel considered that in the circumstances there was insufficient evidence about how and when the complainant had received the document in question. The matter could not be pursued further and no breach of the Code was ruled.

A hospital pharmacist complained about a four page document entitled 'The treatment of allergic conditions' which had been issued by Schering-Plough Ltd. The document was subtitled 'The use of Clarityn and Nasonex in patients with seasonal allergic rhinitis and perennial rhinitis, and Clarityn in urticaria'. The document itself was undated, though the date of revision of the prescribing information for each product was stated.

COMPLAINT

The complainant believed that the document provided doctors and pharmacists with misleading, and indeed incorrect, information.

The complainant had been asked to prepare an evaluation of nasal corticosteroid sprays for the trust's drugs and therapeutics committee and in particular Nasonex versus Flixonase. The issue the complainant had with the document was the table comparing the cost of nasal steroid sprays and the number of metered doses per unit, leading to a comparative cost per day. Fluticasone propionate was listed as containing 120 metered doses whereas in reality it was available as a 150 metered dose size [at the same price]. This clearly altered the cost per day making fluticasone 30p per day rather than 38p. Fluticasone was therefore the cheaper product and in all other respects the complainant could see no real difference between the products.

The complainant regarded this promotion document as totally unacceptable and would be most grateful if this complaint was given prompt attention so that the product information could be withdrawn and revised.

RESPONSE

Schering-Plough stated that the document had been designed to assist drugs and therapeutics committees to evaluate Nasonex. The cost per dose of fluticasone was calculated using the 120-dose presentation rather than the current 150-dose presentation. This gave a cost of fluticasone of 38p per day, rather than 30p per day.

The complainant asked the Authority to 'give this complaint your prompt attention so that the product information can be withdrawn and revised'. Schering-Plough said that it would like to reassure the complainant, and the Authority, that the product information was withdrawn and revised in February 2000, as soon as it was made aware of the addition of a 150 unit pack to the fluticasone presentations.

Schering-Plough provided a copy of a letter that went out to its sales force on 14 February 2000 informing them of the change to the primary care group (PCG) document. All PCGs which had received a copy of the earlier, superseded, document were contacted and sent a copy of the new, amended document, a copy of which was provided.

Schering-Plough very much regretted any confusion that had arisen as a result of the change of presentation. It was never the company's intention to mislead health professionals as to the real cost of fluticasone. It had amended all of its promotional material as soon as it became aware of the change.

Comments on the above were invited from the complainant.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant stated that she was pleased that Schering-Plough had amended the document. The complainant noted that a letter was sent out to the GP sales force about the document amendment in February 2000. The complainant did not prepare the evaluation of Nasonex until well after April and questioned whether the hospital sales force were sent the same letter with the amended document. Either way, the complainant's view was that out-of-date information had been supplied.

The complainant was satisfied that Schering-Plough would amend its company guidelines on medical representatives, updating product literature, and did not feel there was any purpose in pursuing this further. The complainant did not want to be identified to Schering-Plough and as far as the complainant was concerned the document had been changed and the matter was finished.

Comments on the above were invited from Schering-Plough.

FURTHER COMMENTS FROM THE RESPONDENT

Schering-Plough confirmed that the letter of 14 February informing representatives that the document had been updated had been sent to all representatives responsible for promoting Nasonex and Clarityn in hospitals and GP surgeries. The term 'GP sales force' was an abbreviation for the sales force of the GP business unit.

PANEL RULING

The Panel noted that the complainant had started the

evaluation of nasal corticosteroid sprays after April; the amended document had been issued in February.

The Panel noted that it was difficult to progress the matter any further as the complainant's view was that out-of-date information had been supplied but was not willing to be identified to Schering-Plough. The company could not investigate the matter further as it could not identify who had given the document to the complainant. It was difficult to establish exactly what had happened.

The Panel noted that Schering-Plough had updated the document once the presentation of Flixonase had changed. Representatives had been instructed to withdraw the document and a replacement had been issued.

The Panel considered that in the circumstances there was insufficient evidence about how and when the complainant had received the document in question. The matter could not be pursued further and no breach of the Code was ruled.

During its consideration of this case the Panel noted that neither the original document nor the amended document included the date of preparation as required by Clause 4.7 of the Code. This needed to be corrected forthwith. The dates on which the prescribing information for Clarityn and Nasonex had been revised were given but not the date of preparation of the piece as a whole. This might well have contributed to the situation. The Panel requested that Schering-Plough be advised of its concerns.

Complaint received **20 November 2000**

Case completed **27 February 2001**

SANOFI-SYNTHÉLABO v UCB PHARMA

Promotion of Keppra

Sanofi-Synthélabo complained about an advertisement for Keppra which had been placed by UCB Pharma SA, Belgium, in the European edition of the New England Journal of Medicine. Sanofi-Synthélabo stated that the journal was subject to the Code and it was concerned that the advertisement consisted of more than two consecutive pages, that the cost of the product was not stated in the prescribing information and that the claim 'New Keppra: makes treating and living with epilepsy easier' was a hanging comparison.

The Panel noted that it first had to decide whether the advertisement was subject to the UK Code. The supplementary information to Clause 1.1 headed 'Journals with an International Distribution' stated that 'International journals which are produced in English in the UK are subject to the Code even if only a small proportion of their circulation is to a UK audience'. The Panel noted that the advertisement had appeared in the UK run of the European edition of the New England Journal of Medicine. The Panel considered that advertisements in that particular run of the journal were subject to the Code.

The advertisement had been placed by UCB SA, Belgium. It was an established principle under the Code that companies in the UK were responsible under the Code for the activities of their overseas parents. UCB Pharma in the UK was thus responsible under the Code for the advertisement.

UCB accepted that the advertisement consisted of more than two consecutive pages. The Panel ruled a breach of the Code. The Panel noted that the prescribing information did not state the cost of the product. A further breach of the Code was ruled.

The Panel considered that the claim 'New Keppra: makes treating and living with epilepsy easier' was a hanging comparison. UCB's submission that the claim was qualified by bullet points beneath it was not accepted. A breach of the Code was ruled. Upon appeal by UCB, the Appeal Board's view was that the claim clearly compared Keppra with something; the comparator was not stated. The Appeal Board considered that the claim was a hanging comparison and upheld the Panel's ruling of a breach of the Code.

Sanofi-Synthélabo complained about an advertisement (ref KGL12822/KGL10792) for Keppra (levetiracetam) which had been placed by UCB Pharma SA, Belgium in the 2 November issue of the European edition of the New England Journal of Medicine.

COMPLAINT

Sanofi-Synthélabo stated that the journal was produced in English in the UK and was therefore subject to the Code. Sanofi-Synthélabo had a number of concerns.

1 The Code stipulated that no journal advertisement should occupy more than two consecutive pages. The advertisement in question occupied three consecutive pages and Sanofi-Synthélabo alleged a breach of Clause 6.1 of the Code.

2 The prescribing information on the third page contained no information about the cost of the product and Sanofi-Synthélabo alleged that this was clearly in breach of Clause 4.2 of the Code.

3 On the second page of the advertisement the claim was made that Keppra 'makes treating and living with epilepsy easier'. In this claim no attempt was made to compare Keppra to any other medicine and Sanofi-Synthélabo alleged that this was a hanging comparison and in breach of Clause 7.2 of the Code.

RESPONSE

UCB Pharma Limited stated that the regulations relating to promotion were somewhat different in most of Europe when compared to the UK Code. This promotional item was placed in the European edition of the New England Journal of Medicine by UCB Pharma's parent company in Belgium (UCB SA). The material was placed in the belief that the UK Code would not apply as the majority of the circulation was outside the UK. It was thought that European regulations would apply. UCB responded in turn to the allegations.

1 The breach of Clause 6.1 of the Code was accepted.

2 More than 85% (circulation figures provided) of the circulation of the European edition of the New England Journal of Medicine was outside the UK. Therefore the sub-section of Clause 4.2 relating to the requirement to display the cost did not apply.

3 The claim 'New Keppra: makes treating and living with epilepsy easier' was not a hanging comparison. Clearly this statement was not to be taken in isolation but had to be read in the light of the licensed indication, as clearly stated at the top of the promotional piece (for adjunctive therapy for partial seizures in adults), as well as of the three bulleted statements found below the claim, which together supported it. Moreover, these claims were in close proximity to the contested claim and were duly referenced. They were therefore clearly supportive.

* * * * *

On receipt of the complaint the Authority wrote to the communications agency responsible for accepting advertising in the UK edition of the New England Journal of Medicine to clarify in which edition of the journal the advertisement had appeared. The agency explained that the European edition of the journal was split into a number of country specific runs – all of which were referred to as the European edition on the front cover. The different country versions, however, could be identified by a code on the label carrier. If the wrap and label carrier were no longer

with the journal the intended country of distribution could be identified by a similar code on the subscription insert cards. The country specific editions would contain any advertisements scheduled to run in the International as well as European editions along with any country specific advertising that might be booked.

* * * * *

PANEL RULING

The Panel noted that the first issue to be decided was whether the advertisement was subject to the UK Code. The supplementary information to Clause 1.1 headed 'Journals with an International Distribution' stated that 'International journals which are produced in English in the UK are subject to the Code even if only a small proportion of their circulation is to a UK audience. It is helpful in these circumstances to indicate that the information in the advertisement is consistent with the UK marketing authorization'.

The Panel noted that the advertisement had appeared in the UK run of the European edition of the New England Journal of Medicine. The Panel considered that advertisements in that particular run of the journal were therefore subject to the UK Code.

The Panel noted that the advertisement was placed in the journal by UCB SA, Belgium. The Panel noted that it was an established principle under the Code that companies in the UK were responsible under the Code for the activities of their overseas parent company or divisions. The advertisement in question had been placed by UCB Pharma's parent company. UCB Pharma in the UK was therefore responsible under the Code for the advertisement.

The Panel noted that the advertisement consisted of three consecutive pages; a double page spread followed by the prescribing information on page 3. Clause 6.1 of the Code stated that no single advertisement included in a journal could consist of more than two consecutive pages. A breach of Clause 6.1 was therefore ruled.

The Panel noted that Clause 4.1 required prescribing information to appear on all promotional material; the content of prescribing information was set out in Clause 4.2. The Panel noted that the prescribing information in the advertisement did not state the cost of the product and so did not meet all of the requirements set out in Clause 4.2. The advertisement was therefore in breach of Clause 4.1 and a breach of that clause was ruled.

The Panel noted that the supplementary information to Clause 7.2 stated that hanging comparisons whereby a medicine was described as being better or stronger or such like without stating that with which the medicine was compared must not be made. The Panel considered that the claim 'New Keppra: makes treating and living with epilepsy easier' was ambiguous. It could be read to mean that the introduction of the new medicine generally made the treatment of epilepsy less difficult. In the Panel's view, however, some readers would see the claim as a

hanging comparison ie Keppra made treating and living with epilepsy easier than with another medicine which was not stated. The Panel did not accept that the claim was qualified by the bullet points beneath it as submitted by UCB. A breach of Clause 7.2 was ruled. This was appealed by UCB.

APPEAL BY UCB PHARMA

UCB stated that the claim was not a hanging comparison in the context of Keppra's licensed indication (for adjunctive therapy for partial seizures in adults). The indication was clearly stated at the top of the promotional piece. When used within the licensed indication Keppra would be added to existing therapy in patients who had refractory epilepsy. This statement meant that Keppra made treating and living with epilepsy easier than either placebo or no adjunctive treatment. It was stating that use of Keppra as an adjunctive treatment made living with partial epilepsy easier because of the proven reduction of seizure frequency. Treatment was easier because of the favourable pharmacokinetics, efficacy and tolerability of the medicine.

UCB added that the claim should not be taken in isolation. The four bulleted statements found below the claim supported it. They were in close proximity to the contested claim and so the company suggested that they were supportive.

The four bulleted points provided significant supportive evidence. As well as these statements there was a substantial core of evidence relating to Keppra that supported the claim in question.

UCB considered each part of the claim in turn.

'New Keppra: Makes treating ... epilepsy easier'

i) There were no known drug-drug interactions. The pharmacokinetic properties predicted a low potential for interactions (Patsalos 2000).

'Specifically, when evaluated against carbamazepine, phenytoin, valproate, lamotrigine, phenobarbitone, primidone and gabapentin there was no effect on the drug concentration. Formal drug studies against warfarin, digoxin, ethinyloestradiol and levonorgestrel, as well as probenecid showed no interaction'.

ii) Other drug-drug interactions were unlikely as Keppra was <10% protein bound; it was excreted renally. Ninety-three percent was excreted in 24 hours, 66% unchanged, 27% as inactive metabolites and there was no effect of Keppra on CYP 450 isoenzymes, epoxide hydrolase and uridine S-diphosphoglucuronyl transferase (Nicolas *et al* 1999).

iii) Because of the complete and linear absorption, plasma levels could be predicted from the oral dose. This meant that there was no need to monitor the plasma levels of Keppra (summary of product characteristics (SPC)).

iv) Other pharmacokinetic properties of Keppra tended to make treating epilepsy easier: absolute oral bioavailability was nearly 100%; steady state plasma concentrations were generally attained after two days. The steady state pharmacokinetics were predictable and linear and the extent of absorption was not affected by food (SPC).

v) To suggest that a medicine made treating a given condition easier, it must be demonstrable that the side effect profile was acceptable. Clearly if a medicine had a significant number of serious adverse events necessitating dose adjustments or withdrawal in a significant proportion of patients then this claim would be invalid. The evidence suggested that Keppra had a favourable/acceptable side effect profile within the therapeutic area: as yet there had been no known association with idiosyncratic events (data on file); taking pooled data from pivotal trials, the commonest adverse events (where the event was statistically significant to placebo) were somnolence (14.9% Keppra vs 9.7%) and dizziness (13.2% vs 7.4%) and the proportion of patients withdrawing or reducing the dose due to adverse events was 15% for Keppra and 11.6% for placebo (Shorvon *et al* 1999). There was no statistically significant difference between the two groups (data on file).

'New Keppra makes ... living with epilepsy easier.'

UCB stated that again this statement must be taken in the context of the licensed indication. For those suffering with refractory partial seizures, an adjunctive treatment would be expected to make living with epilepsy easier if trials showed statistically significant reductions in seizure frequency (including leading to seizure freedom in a proportion of cases).

The evidence from three large multicentre placebo controlled trials was as follows:-

Shorvon *et al* (2000) (N051; European Trial). This was a randomised double-blind controlled trial of levetiracetam 1000mg and 2000mg bd used as adjunctive therapy in refractory partial onset seizures. The intention to treat (ITT) population was 324. The evaluation period was 12 weeks. Thirty-two percent of patients taking 2000mg/d had >50% seizure reduction (10% in the placebo group, p<0.001). The commonest adverse events were asthenia, headache, accidental injury and somnolence. The total incidence of adverse events in the levetiracetam and placebo group was similar.

Cereghino *et al* (2000) (N132; US trial). The design was very similar to N051, with the exception that the doses used were 1000mg/day or 3000mg/day for levetiracetam. The ITT group was 294. In the placebo group 11% had a ≥50% response and there was no seizure freedom. In the 1000mg group 33% had a ≥50% response (p<0.001) and 3% became seizure free (NS). For 3000mg 40% had a 50% responder rate and 9% became seizure free (p<0.001). Somnolence and dizziness were the commonest adverse effects. These were mild to moderate and rarely led to withdrawal.

Ben-Menachem *et al* (2000) (N138; European Trial). In this trial the ITT group was 286. Randomisation was to placebo or 3000mg. Eighty-six were withdrawn to

monotherapy, 42% of those receiving levetiracetam responded at ≥50%, while 8% were seizure free (placebo was 17% and none, p=<0.001). Discontinuation rates were identical (9% in each group). The commonest adverse events were asthenia, infection (mostly the common cold) and somnolence.

Shorvon *et al* (1999) pooled the results. The response rates (≥50% reduction in partial seizures) were 12.6%, 27.7%, 31.6% and 41.3% for placebo, 1, 2 and 3g respectively. Pooled data for adverse events had already been discussed.

UCB stated that evidence also existed about the longer-term experience with levetiracetam:

Ben-Menachem (2000) looked at whether the long-term efficacy was sustained. Data on 1422 patients were collated. The median duration of exposure was 399 days. Fifty percent responder rates were 39%, 8% were seizure free for at least one year and 13% for at least six months (based on an ITT population).

Krakow *et al* (2000) considered the long term retention rates in the same population. The mean duration of exposure was 622 days. The levetiracetam retention rate was estimated to be 60% after the first year, 37% after 3 years and 32% after 5 years.

UCB stated that finally the promotional piece should be taken in context of the therapeutic area. It was well recognised that treating refractory epilepsy was not an easy matter (Oxbury 2000). Drug interactions and adverse events associated with the use of anti-epileptic medicines remained a challenge to the clinician (Mattson 1998). UCB suggested that the claim in question was not a hanging comparison but was a reasonable claim that was well supported.

APPEAL BOARD RULING

The Appeal Board noted the submission that Keppra was primarily promoted to hospital specialists; it was one of a number of medicines used to treat patients with refractory epilepsy.

In the Appeal Board's view the claim clearly compared Keppra with something. It was not clear whether the comparator was placebo, no adjunctive treatment or other medicines. The comparator was not stated. The Appeal Board considered that the claim was a hanging comparison and upheld the Panel's ruling of a breach of Clause 7.2 of the Code. The appeal was unsuccessful.

Complaint received 22 November 2000

Case completed 1 March 2001

PHARMACIA v GALEN

Promotion of Regurin

Pharmacia complained about a bookmark promoting Regurin (trospium) issued by Galen. The bookmark was headed 'Home & Dry' beneath which there was a photograph of a man and woman disembarking from a boat. The brand name and generic name appeared beneath the photograph. This was followed by the claim 'Reassuringly effective in bladder instability'.

Pharmacia alleged that the claim was inaccurate, unbalanced and misleading. The word 'Dry' created the impression that treatment with Regurin would result in patients having no symptoms of incontinence which was not so.

The Panel did not accept Galen's submission that the phrase 'Home & Dry' was not an absolute statement linked to the product. The Panel noted the data referred to by the parties. The Panel considered that the claim 'Home & Dry' in association with the promotion of Regurin created the impression that treatment with Regurin would result in patients having no episodes of urinary incontinence. This was not so. The claim was misleading. A breach of the Code was ruled. Galen appealed the Panel's ruling.

The Appeal Board noted the company's submission that the phrase 'Home & Dry' related to the patients' improved quality of life; the couple depicted had, due to their increased mobility, been able to undertake an activity, sailing, which they otherwise might not have been able to do. The Appeal Board also noted Galen's submission that doctors were unlikely to interpret the phrase literally. In the context of the bookmark the phrase 'Home & Dry' would not lead a general practitioner to consider that a patient would achieve 100% dryness with Regurin; it was not misleading in this regard. The Appeal Board ruled no breach of the Code.

Pharmacia Limited complained about a leaflet (a bookmark) (ref 1450/2000) for Regurin (trospium) issued by Galen Limited.

The bookmark was headed 'Home & Dry' beneath which there was a photograph of a man and woman disembarking from a boat. The brand name and generic name appeared beneath the photograph. This was followed by the claim 'Reassuringly effective in bladder instability'.

COMPLAINT

Pharmacia alleged that the prominent claim 'Home & Dry', which was reinforced at the bottom of the bookmark by the words 'Reassuringly effective in bladder instability', was in breach of Clause 7.2 of the Code in that it was inaccurate, unbalanced and misleading.

Pharmacia considered that the use of the word 'Dry' was not strictly accurate and might mislead medical practitioners. According to a publication by Füsgen and Hauri (2000), referred to in the promotional item, only '30% of the patients under trospium chloride treatment did not need any further pads or devices'. This inferred that in excess of two thirds of patients on Regurin were not 'dry'.

In communication with Galen, Galen had argued 'that this should be reviewed within its context ie the well recognised phrase 'Home & Dry', which is clearly related to the picture and not to any specific product claims'. In Galen's opinion 'the use of the phrase 'Home & Dry' is clearly not providing information, a claim or a comparison with regard to Regurin and therefore this clause does not apply'.

Pharmacia referred to Case AUTH/949/10/00 where it was found to be in breach of Clause 7.2 of the Code for the use of the phrase 'Freed by Detrusitol'. The word 'Freed' was considered to be 'an absolute term and the claim created the impression that treatment with Detrusitol would result in patients having no symptoms of urgency, frequency or urge incontinence which was not the case'.

On that basis 'Dry' was also an absolute term and created the impression that treatment with Regurin would result in patients having no symptoms of incontinence, which was not the case. As mentioned in the study to which Galen referred, only 30% of patients treated with Regurin no longer required pads or devices.

RESPONSE

Galen stated that the Regurin bookmark had been utilised as a summary of the key product benefits and left with general practitioners and hospital consultants by Galen's medical representatives who would have fully detailed the product and answered any questions raised by the doctor concerned.

Regurin was indicated for the treatment of detrusor instability or detrusor hyperreflexia with the symptoms of urinary frequency, urgency and urge incontinence. The clinical evidence which supported the product licence application demonstrated that trospium was as efficacious as the existing anticholinergic treatments and as well tolerated (especially in terms of the major adverse effect ie dry mouth) as the newer agents, such as tolterodine. From the discussion Galen had had with Pharmacia and the content of its complaint, Galen assumed that this view was accepted.

Galen and Pharmacia were also in agreement with the effect that urinary incontinence had on the quality of life experienced by patients, particularly with regard to frequency and urgency of micturitions. The evidence relating to improving quality of life was outlined by Pharmacia as part of its submission in Case AUTH/949/10/99, where the Panel accepted that tolterodine had been shown to help improve quality of life, although the clear indication was that the evidence was not absolute, as patients continued to report some degree of bladder problems.

In the review article by Füsgen and Hauri quality of life was shown to be improved in a number of studies after treatment with Regurin. As with the clinical

studies on tolterodine, there was no complete elimination of symptoms. However, the reduction in frequency and urgency of micturition would enable many patients to become involved once again in leisure activities, which might not have been possible prior to treatment.

The essence of the promotional campaign for Regurin focused on the assistance this product might give to patients in providing the confidence to undertake day to day and leisure activities which might not have been possible when they had been suffering from a higher frequency of micturition.

The headline used to convey this concept was 'Home & Dry', which appeared to be the main source of contention for Pharmacia as it had equated it to its own headline 'Freed by Detrusitol'. Galen was of the opinion that the two statements were fundamentally different and therefore would not be subject to the same ruling. As ruled, 'Freed by Detrusitol' suggested an absolute guarantee of efficacy related directly to the product. This statement was closely linked to the product claims which further supported the ruling that the efficacy of the product was overstated. Expectations were also raised by the amount of public relations activities associated with the product and therapy area at that time.

By contrast, Galen's headline 'Home & Dry' was a well-recognised figure of speech and not an absolute statement linked directly to the product. Medical practitioners receiving this bookmark would be fully able to distinguish the difference between figure of speech and a product claim, particularly in relation to its proximity to the picture of a middle aged couple disembarking from a boat.

In none of Galen's promotional literature or detail presentation was the phrase 'Home & Dry' linked directly to the product or product claims.

There was an obvious play on the words 'Home & Dry' which suggested that patients on Regurin had the confidence to enjoy regular leisure activities once again, but Galen was confident that no medical practitioner would interpret this literally ie that every patient on Regurin was expected to return home dry. In Galen's experience, both hospital consultants and general practitioners were fully aware of the limitations of antimuscarinic drugs in the treatment of urinary incontinence, which had been confirmed through experiences with the newer agents. Galen's promotion of Regurin placed it realistically into context within the expectations associated with these types of products.

The stab points and related references on the leavepiece were, Galen believed, an accurate reflection of the product benefits and the clinical evidence to support the statements. All of these references were readily available to healthcare professionals on request.

In conclusion, therefore, Galen was of the opinion that 'Home & Dry' was a common figure of speech which, as far as medical practitioners were concerned, would not be taken literally as a product claim. Galen submitted that, with the context in which it appeared 'Home & Dry' could in no way be seen as inaccurate,

unbalanced and misleading, and therefore was not in contravention of Clause 7.2 of the Code.

PANEL RULING

The Panel did not accept Galen's submission that the phrase 'Home & Dry' was not an absolute statement linked to the product. The Panel noted the data referred to by the parties. The Panel considered that the claim 'Home & Dry' in association with the promotion of Regurin created the impression that treatment with Regurin would result in patients having no episodes of urinary incontinence. This was not so. The claim was misleading. A breach of Clause 7.2 of the Code was ruled.

APPEAL BY GALEN

Galen stated that it remained of the opinion that there was a fundamental difference between the use of the phrase 'Home & Dry' in the promotion of Regurin and the 'Freed by Detrusitol' claim employed by Pharmacia. In the latter case the brand name was inextricably linked to the claim, which had been considered to be an absolute term.

In the case of Regurin, however, the headline, which accompanied the photograph, conveyed the fact that patients taking Regurin were able to enjoy an improved quality of life based on decreased restrictions in leisure activities (Füsgen and Hauri). In contrast, the claim linked to Regurin was 'reassuringly effective in bladder instability', which was supported by the product's proven efficacy in treating urinary frequency, urgency and urge incontinence. This claim was based on the clinical evidence referenced on the reverse of the bookmark.

In addition, 'Home & Dry' was a well-recognised phrase in everyday use. Given the educational and professional attributes of medical practitioners, Galen was of the opinion that they were able to distinguish between a 'play on words' using this type of common phrase and definitive product claims. This differentiation was further assisted by the layout, which positioned 'Home & Dry' alongside the photograph, which reflected that phrase within a recognisable context; furthermore, the product claims were placed in close proximity to the brand name, both on the front and back of the bookmark. Galen argued that this statement should not be regarded as misleading, as medical practitioners would not be expected to interpret it as a claim for the product. This contrasted sharply with the inextricable link between claim and product in the phrase 'Freed by Detrusitol'.

From a review of current advertising in medical journals, Galen had noted a number of advertisements in which common phrases or 'plays on words' had been employed examples were provided.

APPEAL BOARD RULING

The Appeal Board noted the company's submission that the phrase 'Home & Dry' related to the patients' improved quality of life; the couple depicted had, due to their increased mobility, been able to undertake an activity, sailing, which they otherwise might not have

been able to do. The Appeal Board also noted Galen's submission that doctors were unlikely to interpret the phrase literally. In the context of the bookmark the phrase 'Home & Dry' would not lead a general practitioner to consider that a patient would achieve 100% dryness with Regurin; it was not misleading in

this regard. The Appeal Board ruled no breach of Clause 7.2. The appeal was successful.

Complaint received **23 November 2000**

Case completed **8 February 2001**

CASE AUTH/1108/11/00

AVENTIS PASTEUR MSD v SMITHKLINE BEECHAM

Engerix B promotional poster

Aventis Pasteur MSD complained about an Engerix B poster issued by SmithKline Beecham Pharmaceuticals. The poster was aimed at health professionals to be displayed in treatment rooms.

Aventis Pasteur MSD alleged that the statement 'One in 125 travellers to hepatitis B endemic areas contract HBV – a greater risk than catching flu in the UK during an epidemic (400:100,000)' was inaccurate and misleading. Although SmithKline Beecham had conceded that it had made an error and the figure should have been 1 in 625, Aventis Pasteur MSD alleged that this was still an over-exaggeration and likely to cause patients and healthcare professionals unnecessary anxiety, particularly with the reference to a common disease such as influenza. The statement was unbalanced because the figure quoted referred to hepatitis B in expatriates who, due to their length of stay, had a risk that was clearly greater than the average traveller. A paper specifically examining hepatitis B in travellers estimated a risk of 1:2500 for hepatitis B in returning travellers; this included a correction for 50% under-reporting. The Panel noted that it was difficult to accurately determine the precise risk of contracting HBV. The Panel noted that SmithKline Beecham had acknowledged that the figure in the poster was wrong and a breach of the Code was ruled. Given the apparent inability to determine a more precise figure than something between 1 in 625 and 1 in 2500, the Panel queried whether an absolute figure should have been included in the poster which was aimed at non-specialists; in the Panel's view the intended audience was unlikely to appreciate the difficulties associated with calculating the precise risk of contracting HBV. The Panel requested that both companies be advised of its concerns.

Aventis Pasteur MSD alleged that the claim 'Delivers unbeaten* long term protection against hepatitis B.....' was a hanging comparison. Even taking the footnote into consideration, it was unreferenced and not supported by any data of which Aventis Pasteur MSD was aware. SmithKline Beecham had acknowledged that the claim was not based on any data, but stated that it was not aware that Engerix B had been shown to be inferior to other hepatitis B vaccines in this regard. Aventis Pasteur MSD did not believe that this rendered the claim supportable, particularly since it implied that Engerix B had some special merit compared to other hepatitis B vaccines. The Panel considered that the claim was not for superiority. The claim implied that no other hepatitis B vaccine delivered better long term protection than Engerix

B but did not exclude the possibility that another vaccine might deliver equivalent long term protection. The Panel noted that SmithKline Beecham had submitted a number of studies to support the claim. No data had been supplied by Aventis Pasteur MSD to demonstrate that any other treatment was more effective than Engerix B. The claim was not one that required a reference. The Panel did not consider that the claim constituted a hanging comparison as alleged. Nor was the claim for unbeaten long term protection unacceptable. No breach of the Code was ruled.

Aventis Pasteur MSD alleged that the statement 'Strength of immune memory is dependent on antigen dose from primary course' was unbalanced and misleading because antigen structure, as well as dose, affected vaccine immunogenicity. It left the impression that a vaccine whose dose was lower would result in a weaker memory response. The Panel noted that the scientific poster to which the claim was referenced stated as one of its conclusions 'Vaccine antigen dose and structure influence the primary antibody response and development of immune memory'. The abstract of the subsequent paper stated that 'Vaccine antigen dose and structure have been identified as important influences in the primary antibody response and development of immune memory'. The Panel considered that the statement by only referring to one of the factors that was important with regard to strength of immune memory was misleading. A breach of the Code was ruled.

Aventis Pasteur MSD Ltd complained about a promotional poster (ref EBLP/00/36) issued by SmithKline Beecham Pharmaceuticals which related to Engerix B (hepatitis B vaccine). The poster was headed 'Hepatitis B Your guide to travellers at risk'. Aventis Pasteur MSD had been in correspondence with SmithKline Beecham but its concerns had not been adequately addressed.

SmithKline Beecham stated that the poster was aimed at health professionals and was displayed in treatment rooms. The posters were distributed by SmithKline Beecham's vaccine sales representatives who had been briefed on how to discuss its contents with their customers.

1 Statement 'One in 125 travellers to hepatitis B endemic areas contract HBV – a greater risk than catching flu in the UK during an epidemic (400:100,000)'

This appeared under the heading 'Key Facts'

COMPLAINT

Aventis Pasteur MSD alleged that the statement breached Clause 7.2 of the Code because it was inaccurate and misled on the necessity for vaccination by implication.

The reference cited (Steffen *et al* 1994) was entitled 'Epidemiology and Prevention of Hepatitis A in Travelers', although it also contained a small amount of information about hepatitis B. SmithKline Beecham had obtained this figure by extrapolating the mid-point in Table 2 of the paper. Although SmithKline Beecham conceded that it had made a calculation error, now making the figure 1 in 625, Aventis Pasteur MSD alleged that this was still an over-exaggeration and likely to cause unnecessary anxiety amongst patients and healthcare professionals, particularly with the reference to a common disease such as influenza. The statement was unbalanced because the figure quoted referred to hepatitis B in expatriates who, due to their length of stay, had a risk that was clearly greater than the average traveller. Were no other figures available, it might be defensible to refer to expatriates. However, this was not the case. A paper by the same author, specifically examining hepatitis B in travellers, was available. This estimated a risk of 1:2500 for hepatitis B in returning travellers. This included a correction for 50% under-reporting. Aventis Pasteur MSD did not find the reference to under-reporting in SmithKline Beecham's response to the company convincing since it was well recognised that the incidence of asymptomatic disease in infants was much higher than in adults.

RESPONSE

SmithKline Beecham stated that it had already acknowledged that this figure should have been 1 in 625 and offered to amend the poster. The complainant however argued that the figure of 1 in 625 was based on a study conducted among expatriates, who had a risk that was higher than that of the average traveller, and quoted a different study by the same author, in non-expatriate travellers (Steffen 1990), which cited a risk of 1 in 2500 and included a correction of 50% for under-reporting. Scrutiny of this paper, conducted in Swiss travellers, however, revealed a number of weaknesses which indicated that the level of under-reporting was likely to be significantly greater than 50%. Firstly, only symptomatic infections were included. Only two thirds of adults and one third of older children with hepatitis B had symptomatic disease, although the long term risks (cirrhosis, hepatocellular carcinoma) occurred following both symptomatic and asymptomatic infection. This factor on its own would result in under-reporting of about 50% taking all age groups together.

Secondly, the study was conducted retrospectively and was based on infections identified in travellers after they returned home, and therefore (as acknowledged

by the author) might not have identified patients diagnosed while still abroad, patients in whom no blood sample was submitted for testing, and patients whose samples were tested outside the study region. Thirdly, injecting drug users were excluded from two of the three datasets analysed.

The most robust method of estimating the true incidence, and thereby the level of under-reporting of infections such as hepatitis B, was to undertake a population-based seroprevalence study. Such a study had been conducted in UK children (Hesketh *et al* 1997) and revealed a 200-fold level of under-reporting. These data were sent to the complainant which however now argued that this level of under-reporting was not applicable to adults due to the higher incidence of asymptomatic disease in infants. The study in fact estimated the cumulative annual risk of infection in children between birth and 14 years of age, in whom the proportion of symptomatic disease ranged from 5% at birth to about 50% by 14 years. Thus the level of under-reporting in adults, among whom the proportion of symptomatic disease was about 70%, while it would be less than the figure of 200-fold suggested by Hesketh *et al*, was likely to be significantly higher than the figure of 50% (2-fold) suggested by Steffen. On this basis SmithKline Beecham submitted that an estimate of 1 in 625 travellers was defensible.

PANEL RULING

The Panel noted that it was difficult to determine the precise risk of contracting HBV with accuracy. The Panel noted that the figure in the poster referred to hepatitis B in expatriates and, according to Aventis Pasteur MSD, due to their length of stay they had a risk that was greater than the average traveller. The poster stated that in hepatitis B endemic areas the risk to travellers was 1 in 125; SmithKline Beecham had acknowledged that this figure was wrong and should have been 1 in 625. The Panel ruled a breach of Clause 7.2 of the Code.

The Panel noted Aventis Pasteur MSD's view that the poster should have stated that the risk of a traveller contracting HBV was 1 in 2500 and its comments about the relevance of data on expatriates. The paper from which that figure was taken (Steffen 1990) had included a correction for 50% under-reporting. Another paper (Hesketh *et al*) had revealed a 200-fold level of under-reporting in a group of UK children. Given the apparent inability to determine a more precise figure than something between 1 in 625 and 1 in 2500, the Panel queried whether an absolute figure should have been included in a poster which was meant to be displayed in general practice treatment rooms. The poster was aimed at non-specialists; in the Panel's view the intended audience was unlikely to appreciate the difficulties associated with calculating the precise risk of contracting HBV. The Panel requested that both companies be advised of its concerns.

2 Claim 'Delivers unbeaten* long term protection against hepatitis B.....'

The claim appeared as a subheading to the second section of the poster. The asterisk related to a footnote

at the bottom of the poster which stated 'Compared to other hepatitis B vaccines'.

COMPLAINT

Aventis Pasteur MSD alleged that this claim breached Clauses 7.2 and 7.8 of the Code. Despite the asterisk following 'unbeaten' this was a hanging comparison. Even taking the footnote into consideration, it was unreferenced and not supported by any data of which Aventis Pasteur MSD was aware. Indeed SmithKline Beecham acknowledged in its response that the claim was not based on any data, but that it was not aware that Engerix B had been shown to be inferior to other hepatitis B vaccines in this regard. Aventis Pasteur MSD did not believe that this rather nihilistic response rendered the claim supportable, particularly since it implied that Engerix B had some special merit compared to other hepatitis B vaccines. The need to demonstrate superiority rather than non inferiority was illustrated by the ruling in Case AUTH/953/11/99.

RESPONSE

SmithKline Beecham did not accept this allegation. It provided a table which summarised the principal findings of studies that directly compared the immunogenicity of Engerix B and the complainant's recombinant hepatitis B vaccine. None of these studies had shown Engerix B to be inferior, and in some of the studies the antibody titre was higher with Engerix B than with the complainant's vaccine. Most of the studies were small, but two of the larger studies were worthy of more detailed comment. Firstly, a US multi-centre, double-blind, randomised clinical trial in 460 older subjects (aged 39-70 years) reported that immunisation with Engerix B (20µg) resulted in higher titres of anti-HBs at the completion of vaccination when compared with the complainant's recombinant vaccine (10µg) (Treadwell *et al* 1993). Secondly, an epidemiological study from the Minnesota Department of Health indicated that in 595 health care workers who received hepatitis B vaccine, after controlling for smoking status, gender, age and body mass index, recipients of the complainant's recombinant vaccine were more likely to lack anti-HBs than recipients of Engerix B (relative risk, 2.3, 95% confidence interval 1.1 to 4.7; p=0.02). The authors speculated that 'the difference in the anti-HBs seronegativity rates following vaccination from recipients of the vaccines is likely due to the different amount of HBsAg protein per dose of [Aventis Pasteur] MSD's recombinant vaccine compared with Engerix B' (Wood *et al* 1993).

In addition to these comparative studies, an independent 1998 ADIS drug evaluation of Engerix B (Adkins and Wagstaff 1998) commented that 'comparison of the 2 vaccines at their recommended dosages showed that [Engerix B] 20 µg generally produced a more rapid immune response and higher anti-HBs geometric mean titres at completion of the vaccination schedule than [the complainant's recombinant vaccine] 10µg'.

More recently André *et al* (2000) conducted a meta analysis of published clinical trials on Engerix B and the complainant's recombinant vaccine. This involved 181 publications and almost 33,000 subjects vaccinated

(over 24,000 with Engerix B). Both vaccines produced excellent seroprotective response rates in normal healthy subjects (around 95%). A somewhat lower response rate was however found with the complainant's recombinant vaccine compared with Engerix B in health care workers, infants and the 'at risk' population (drug users, haemophiliacs, homosexuals). The author commented that this might reflect the lower antigen content of the complainant's recombinant vaccine.

In summary, the weight of scientific evidence, in SmithKline Beecham's opinion, clearly supported the view that Engerix B delivered superior protection to that of the complainant's product. SmithKline Beecham knew of no evidence which showed that long term protection afforded by Engerix B had been beaten by any other agent.

PANEL RULING

The Panel noted that in Case AUTH/953/11/99 it considered that the claim 'Unmatched service and support' was exaggerated and ruled a breach of Clause 7.8 of the Code. The claim implied that the services and support offered were better than that offered by any other company; no data was submitted to support this position. The claim was one for superiority. The Panel's ruling was not appealed.

The Panel considered that the claim now before it was different to that considered in Case AUTH/953/11/99. The claim that Engerix B 'Delivers unbeaten long term protection against hepatitis B ...' was not a claim for superiority. The claim implied that no other hepatitis B vaccine delivered better long term protection than Engerix B but did not exclude the possibility that another vaccine might deliver equivalent long term protection. The Panel noted that SmithKline Beecham had submitted a number of studies to support the claim. These demonstrated that at 8-9 months post-dose the seroprotection rates for Engerix B and the Aventis Pasteur MSD product were similar. The geometric mean titres (a measure of the strength of antibody response) were also similar overall. The Panel noted that the review by Adkins and Wagstaff concluded by stating that Engerix B was as effective as other hepatitis B vaccines. No data had been supplied by Aventis Pasteur MSD to demonstrate that any other treatment was more effective than Engerix B. The claim was not one that required a reference.

The Panel did not consider that the claim 'Delivers unbeaten long term protection against hepatitis B' constituted a hanging comparison as alleged. In the Panel's view the claim would be read as being a comparison of Engerix B with other hepatitis B vaccines. The Panel did not consider that the claim for unbeaten long term protection was unacceptable as alleged. No breach of Clauses 7.2 and 7.8 was ruled.

3 Statement 'Strength of immune memory is dependent on antigen dose from primary course'

COMPLAINT

Aventis Pasteur MSD alleged that the statement was unbalanced and misleading and in breach of Clause

7.2 of the Code. It was unbalanced because, as indicated in figure 5 of the scientific poster to which the statement was referenced (Banatvala *et al* 2000), antigen structure, as well as dose, affected vaccine immunogenicity. It was misleading because it left the impression that a vaccine whose dose was lower would result in a weaker memory response. In fact, what the poster showed was that increasing the dose of the same antigen (in this case formalin-inactivated vesicular stomatitis virus) increased the T cell and B cell response. Indeed, this poster provided no data on the T cell and B cell responses to different doses of hepatitis B vaccine.

Aventis Pasteur MSD referred to SmithKline Beecham's view that there were no data comparing the effect of antigen structure between HB-VAX II (Aventis Pasteur MSD's product) and Engerix B. However this was not the case. The differences in antigen structure, which were due to a patented washing process employed during the manufacture of HB-VAX II, almost certainly accounted for the differences in potency between the two vaccines. There were at least two studies comparing identical doses of the two vaccines, demonstrating greater potency for HB-VAX II (Bryan *et al* 1995 and Milne *et al* 1989). Indeed, Milne in a letter on the subject stated that 'The immunising potency of hepatitis B vaccine is not related directly to quantity of antigen. It depends instead on the tertiary structuring of the antigen that specified its quality. It is for this reason that products of two different manufacturers require different amounts of antigen per dose'.

RESPONSE

SmithKline Beecham did not accept this allegation. The statement was supported by a reference to a scientific poster presented at an international symposium, a copy of which had been provided to the complainant. The data had since been published in a peer review journal. The authors concluded that both antigen dose and structure were determinants of immune memory, although in SmithKline Beecham's view greater emphasis was given to the issue of the antigen dose. In an earlier review of the efficacy of different doses of hepatitis B vaccines, the author concluded that the higher dose of vaccine in Engerix B gave a greater immunostimulant effect resulting in longer-lasting protection. No mention was made of antigen structure in this review.

SmithKline Beecham commented on the three references cited by Aventis Pasteur MSD in support of its view that antigen structure was important. The first study was small and none of the differences between vaccines of the same dose were statistically significant. The second study was conducted in children and compared non-conventional doses of vaccine (2µg in each group, whereas the licensed doses in children were 10µg and 5µg for Engerix B and the complainant's vaccine respectively). The third reference was an earlier letter by the same author of the second study, reporting preliminary results of that study, and added no further evidence.

It was thus SmithKline Beecham's view that its poster was neither misleading nor unbalanced, and that the weight of scientific evidence supported the statement.

PANEL RULING

The Panel noted that the scientific poster to which the claim was referenced stated as one of its conclusions 'Vaccine antigen dose and structure influence the primary antibody response and development of immune memory'. The abstract of the subsequent paper by the same authors (Banatvala *et al* 2001) stated that 'Vaccine antigen dose and structure have been identified as important influences in the primary antibody response and development of immune memory'.

The Panel noted that the Engerix B poster included the statement 'Strength of immune memory is dependent on antigen dose from primary course' above a very basic figure showing a straight line relationship between immune memory and antigen dose such that the larger the antigen dose the stronger the immune memory. The Panel noted that each dose of Engerix B was 20µg whereas each dose of HB-Vax II (Aventis Pasteur MSD's product) was only 10µg. The inference of the statement and the figure was that by virtue of its higher dose, Engerix B would produce a stronger immune memory than its competitor product.

The Panel considered that the statement by only referring to one of the factors that was important with regard to strength of immune memory was misleading. A breach of Clause 7.2 was ruled.

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During its consideration of this case the Panel noted that the poster was aimed at health professionals to be displayed in treatment rooms. The poster included the brand name, Engerix B, and made a number of claims for the product. In the bottom right hand corner of the poster was the statement 'Best choice for late presenting travellers'. The Panel queried whether the poster met the requirements of Clauses 7.8 in that the claim 'Best choice ...' was a superlative. The Panel noted that the only date on the poster was 28 June 1999, which appeared at the end of the prescribing information. Three references published in 2000 had, however, been cited in support of some of the claims. The Panel queried whether the poster met the requirements of Clause 4.7 of the Code. The Panel requested that these matters be taken up with SmithKline Beecham in accordance with Paragraph 16 of the Constitution and Procedure (Case AUTH/1149/2/01).

Complaint received 29 November 2000

Case completed 8 February 2001

PHARMACY MANAGER v PFIZER

Outcomes guarantee in a study

A retail pharmacy manager complained about an article in Pulse which referred to a scheme offering GPs a money-back guarantee if Pfizer's product Lipitor (atorvastatin) did not reduce patients' cholesterol levels by an agreed but undisclosed amount. One primary care group (PCG) had signed up but another had refused to join the scheme claiming that the money-back promise would exert excessive influence on GPs' prescribing decisions. The pilot was being evaluated by a university professor. Pfizer had negotiated an expected outcome with the health authority and PCG.

The article reported the professor as saying that if Lipitor did not perform as expected Pfizer refunded the health service for wasted resources; he also stated that the money gave a mechanism locally to optimise the delivery of national service framework targets by getting an open and transparent relationship with the PCG. The article referred to the pilot scheme receiving approval from a local ethics committee on the basis that no money would be refunded until the pilot was over and that GPs must inform patients of the scheme before prescribing Lipitor.

The complainant stated that to him the pilot compromised medical ethics and limited clinical (and appropriate) choice. The complainant and a number of his colleagues considered that it constituted an inducement to prescribe which was prohibited by the Code.

The Panel noted that the pilot study was not quite as described in the Pulse article. The pilot study was to test the feasibility of providing an outcomes guarantee. Potential candidates for cholesterol lowering therapy with statins were to be identified via an audit. The patients were assessed and statin therapy was initiated in accordance with established treatment guidelines. Outcomes were to be monitored. The outcomes guarantee related specifically and only to atorvastatin; the study as a whole encompassed all available licensed statins. The GP decided whether and which statin to prescribe. Pfizer stated that the pilot study would assess outcomes in terms of lowering cholesterol specifically with atorvastatin, but would also assess overall the use of statins in the secondary prevention of CHD.

The Panel noted that in the pilot study the calculations regarding any rebate would be carried out but no payments would actually be made. In the future similar schemes which reimbursed health authorities might be implemented.

The Panel considered that, as a matter of principle, it was not necessarily unacceptable to offer some sort of outcome guarantee with a product. Whether any particular scheme was acceptable or not would depend on the individual arrangements. With the pilot study in question the Panel noted that if payments had been made, they would have been made to the health authority and not to the GPs or the PCG. No individual health professionals would have benefited either directly or indirectly.

The Panel ruled that the pilot study was not in breach of the Code as alleged.

A pharmacy manager at a supermarket complained about what had been described in an article in Pulse, 9 September 2000, as a money-back drug trial and which involved Pfizer Limited and its product Lipitor (atorvastatin).

The article referred to a scheme offering GPs a money-back guarantee if Lipitor did not reduce patients' cholesterol levels by an agreed but undisclosed amount. One primary care group (PCG) had signed up but another had refused to join the scheme claiming that the money-back promise would exert excessive influence on GPs' prescribing decisions. The pilot was being evaluated by a university professor. Pfizer had negotiated an expected outcome with the health authority and PCG.

The article reported the professor as saying that if Lipitor did not perform as expected Pfizer refunded the health service for wasted resources; he also stated that the money gave a mechanism locally to optimise the delivery of national service framework targets by getting an open and transparent relationship with the PCG. The article referred to the pilot scheme receiving approval from a local ethics committee on the basis that no money would be refunded until the pilot was over and that GPs must inform patients of the scheme before prescribing Lipitor.

COMPLAINT

The complainant stated that he wrote out of interest and concern. He was intrigued that one named PCG had already signed up for the pilot which to him compromised medical ethics and limited clinical (and appropriate) choice. The complainant and a number of his colleagues considered that it constituted an inducement to prescribe which he knew was prohibited by the Code.

RESPONSE

Pfizer stated that the article was incorrect in several respects and, in any event, it firmly believed that the pilot study to which it referred was medically and ethically sound and did not breach the Code in any way.

Study outline

Pfizer stated that the study was a pilot project to test the feasibility of providing an 'outcomes guarantee' for Pfizer's cholesterol-lowering product, atorvastatin (Lipitor), to a health authority. The pilot ran in certain general practices within a named health authority. As part of the project, an audit was carried out by a third party in these practices to identify potential candidates for cholesterol lowering therapy with statins, followed by patient assessment, initiation of statin therapy in accordance with established national

treatment guidelines, monitoring of outcomes and comparison against the defined 'outcomes guarantee'. Although the outcomes guarantee related specifically and only to atorvastatin, the study as a whole encompassed all available licensed statins and in no way directed general practitioners to prescribe atorvastatin. The GP decided whether and which statin to prescribe, and at what dose, and the study would assess outcomes in terms of the lowering of cholesterol specifically with atorvastatin but would also assess overall the use of statins in the secondary prevention of coronary heart disease (CHD). The study was managed and evaluated by the staff of a university department and the university had entered into a contract with another company under which the latter provided nurse advisors to carry out the study in the relevant general practices. The study was funded by Pfizer.

Background/origins of the study

Pfizer stated that the university first suggested an 'outcomes guarantee' project in the area of CHD in 1998 and the health authority expressed an interest in such a study in principle. At the same time discussions were initiated between the university and Parke Davis & Co Limited and Pfizer Limited, which were the companies co-promoting atorvastatin at the time. Since then, the companies had merged. CHD presented particular challenges for the health authority, since it had high levels of CHD mortality and yet a low rate of prescribing lipid lowering agents by national standards. The proposed study presented an opportunity to carry out an innovative outcomes research project within the health authority, increase awareness and knowledge of patients and practice staff in this disease area and train practice staff, together with an intervention programme aimed ultimately at improving cholesterol control and therefore cardiovascular outcomes in the health authority's 'at risk' patient population. This was the principal reason for local NHS participation. The health authority's approach to the project concept was illustrated in the presentation given by its then pharmaceutical adviser at the launch meeting for the study in September 1999, which was attended by representatives from all five PCGs within the health authority, the health authority itself and the university. Among the health authority's guiding principles were that the clinical freedom of healthcare professionals should be preserved and that no preference should be given to a particular company or product. Resources could only be accepted from industry on the condition that no single company or product would be endorsed by the health authority. This requirement was key to the way in which the study was designed. Each of the PCGs was invited to participate in the study and, ultimately, two of the health authority's five PCGs chose to do so: two areas which had particularly high CHD mortality within the health authority. In March 2000, both of these PCGs in turn notified their GP practices about the study and invited their participation – this document (prepared by the university and sent out by the PCG boards) was provided.

Documentation/contracts

Pfizer stated that, as mentioned above, the university was conducting the study. Copies of various documents were provided.

The university's proposal, detailing the study, referred to the terms of the outcomes guarantee itself. These were contained in the 'Terms and Conditions of Supply to [named] Health Authority' of atorvastatin dated 19 October 1999, a copy of which was provided. These made clear that the guarantee did not direct choice of medicine by the health authority's healthcare professionals. However, where atorvastatin was used, the product would be guaranteed to achieve certain results in terms of cholesterol lowering in the total study population and, failing the achievement of those targets, a financial rebate would be calculated at the end of the study period. If the product performed to target, there would be no rebate. Any such payment would be made at the end of the study, direct to the health authority. No payment would be made to individual PCGs, general practices or other health authorities. The terms and conditions also made it clear that the guarantee was not dependent upon the prescribing of a certain level of atorvastatin and that there was no other compensation linked to a change in prescribing habits. The terms and conditions contained worked examples of how the guarantee would operate and how the calculation would be worked out.

The study was due to start in September 1999 but the intervention arm of the study was in fact delayed until August 2000 (it was now due to complete by December 2001). The main reason for this delay was the time taken to obtain approval of the local research ethics committee, which was eventually received on 3 August 2000. Whilst the ethics committee approved of the study as such, it was concerned at the requirement that Parke Davis/Pfizer should make a cash reimbursement to the health authority at the end of the project. For this reason, it was agreed with the ethics committee that, on completion of the study, a calculation would be made in accordance with the terms and conditions of supply as to the amount (if any) that would be payable to the health authority, but no such amount would actually be paid within the context of the study. However, the ethics committee did state that if the project proved to be successful, health authorities would then be free to enter into such arrangements in the future. For this reason, whilst terms and conditions of supply did provide the basis for calculation of the 'notional' reimbursement, these terms had been allowed to lapse since the ethics committee's approval did not ultimately allow such a payment within the context of the study.

Compliance with the study

Pfizer stated that the project was a clinical/academic pilot study which, as the documents made clear, was not directional as to the choice of medicine. Healthcare professionals involved had complete clinical freedom to treat their patients according to those patients' best interests in their clinical judgement. It was both supported and carried out by a health authority and an academic unit, with the approval of the local research ethics committee. The study essentially tested the feasibility of providing an 'outcomes guarantee' – by means of evaluating atorvastatin's performance in calculating the notional reimbursement (if any) due at the end – without actually making such a payment. The article had

therefore incorrectly represented the study, suggesting both that payment would be made to GPs/PCGs themselves, which was never the intention, and/or that the refund would actually be made to the health authority, which was also not the case following the terms of the ethics committee's approval. Pfizer therefore firmly believed that no inducement to prescribe atorvastatin had been offered or given in breach of Clause 18.1 of the Code and that the study did not infringe the Code in any way.

In fact, as envisaged by the ethics committee, Pfizer considered that if such a guarantee were actually implemented and appropriate reimbursements made under identical or similar terms to that originally agreed with the health authority in this case, this too would be in compliance with the Code. Indeed, Pfizer was hopeful that, if the study was a success, it might be possible in the future to roll out similar projects and outcomes guarantees with this and/or other health authorities, including actual guaranteed payments as appropriate.

PANEL RULING

The Panel noted that the pilot study was not quite as described in the Pulse article. The pilot study was to test the feasibility of providing an outcomes guarantee. Potential candidates for cholesterol lowering therapy with statins were to be identified via an audit carried out by a third party on behalf of Pfizer. The patients were assessed and statin therapy was initiated in accordance with established treatment guidelines. Outcomes were to be monitored and compared with the defined outcomes guarantee. The outcomes guarantee related specifically and only to atorvastatin; the study as a whole encompassed all available licensed statins. The GP decided whether and which statin to prescribe. Pfizer stated that the pilot study would assess outcomes in terms of lowering cholesterol specifically with atorvastatin, but would also assess overall the use of statins in the secondary prevention of CHD.

The Panel noted that in the pilot study the calculations regarding any rebate would be carried

out but no payments would actually be made. In the future similar schemes which reimbursed health authorities might be implemented.

The Panel noted Clause 18.1 of the Code which stated that no gift, benefit in kind or pecuniary advantage shall be offered or given to members of the health professions as an inducement to prescribe, supply, administer or buy any medicine.

The Panel noted that under the Code there were mechanisms whereby companies could offer additional benefits with medicines even if these might be regarded as inducements to prescribe. In this regard the Panel noted the supplementary information to Clause 18.1 of the Code that measures or trade practices relating to prices, margins and discounts which were in regular use by a significant proportion of the industry on 1 January 1993 were outside the scope of the Code. Other trade practices were subject to the Code. Package deals whereby the purchaser of particular medicines received with them other associated benefits such as apparatus for administration were also acceptable, provided that the transaction as a whole was fair and reasonable.

The Panel considered that, as a matter of principle, it was not necessarily unacceptable to offer some sort of outcome guarantee with a product. Whether any particular scheme was acceptable or not would depend on the individual arrangements. With the pilot study in question, the Panel noted that if payments had been made, they would have been made to the health authority and not to the GPs or the PCG. No individual health professionals would have benefited either directly or indirectly.

The Panel considered that the pilot study was not in breach of Clause 18.1 of the Code and ruled accordingly.

Complaint received **1 December 2000**

Case completed **8 February 2001**

GLAXO WELLCOME v 3M HEALTH CARE

Promotion of Qvar and Airomir

Glaxo Wellcome complained about a number of promotional items relating to Qvar (CFC-free beclomethasone) and Airomir (CFC-free salbutamol) issued by 3M Health Care.

The envelope for a Qvar mailing bore the words 'Chicken soup enclosed' but no wording or logo to indicate that it was from a pharmaceutical company and Glaxo Wellcome alleged that it was thus disguised promotion. The Panel noted that the supplementary information to the Code stated that envelopes must not be used if they bore words implying that the contents were non-promotional. The Panel considered that the text created the impression that the envelope contained promotional material, but promotional material for chicken soup not a medicine. The envelope thus constituted disguised promotion of a medicine and a breach of the Code was ruled.

A sachet of chicken soup was attached to the front cover of the Qvar leaflet. The leaflet explained that historically chicken soup had been recommended for asthma. Glaxo Wellcome stated that it was clear that chicken soup had no relevance to current medical practice. The Panel noted that promotional aids had to be inexpensive and relevant to the practice of the recipient's profession. In the circumstances of this case, as the inherent value of the item was negligible, and as there was some, albeit limited, relevance to the practice of medicine, the Panel decided that the item was not unacceptable and ruled no breach.

Glaxo Wellcome stated that the claim 'Well-validated radiolabelling techniques have demonstrated the superiority of Qvar over conventional beclomethasone (CFC-BDP) and CFC-fluticasone inhalers when it comes to delivering drug to the lungs' clearly implied clinical superiority based on deposition data. However, these data were obtained in healthy volunteers and no evidence had been supplied to suggest that this increase in lung deposition resulted in any proportionate and clinically relevant improvements in asthma control. Glaxo Wellcome alleged that the claim was misleading and had no clinical significance. The Panel noted that whilst the claim was referenced to data in healthy volunteers, there was some comparable data in patients available to substantiate the claim with regard to CFC-BDP. No such data had been submitted with reference to CFC-fluticasone. On balance the Panel considered the claim misleading and a breach of the Code was ruled. Upon appeal by 3M Health Care, the Appeal Board noted that there was some comparable clinical data to substantiate the claim with reference to CFC-BDP. There was no lung deposition data for fluticasone in patients to support that seen in healthy volunteers. The Appeal Board noted 3M Health Care's submission that by using data on fluticasone deposition from a study on healthy volunteers it had presented the best case scenario for delivery of fluticasone to the lungs. Nonetheless the Appeal Board considered the claim misleading and upheld the Panel's ruling of a breach of the Code.

Glaxo Wellcome stated that the all-embracing claim '... when a patient on CFC-BDP or budesonide is symptomatic ...' a doctor '... can simply step over to Qvar without increasing the dose' and thus '... can significantly improve clinical

outcomes for your patients' suggested that all patients symptomatic on CFC-BDP or budesonide could be transferred to Qvar, at the same microgram dose. Glaxo Wellcome stated that this was not so however, as Qvar was not suitable for patients under 12 years of age and any patient symptomatic on CFC-BDP or budesonide at a dose in excess of 800mcg/day. The Panel noted that the maximum recommended dose of Qvar was 800 mcg/day in divided doses. It was not licensed for use in children under 12 years. The Panel considered that the claim gave the impression that all patients symptomatic on CFC-BDP or budesonide could be simply transferred to Qvar at the same microgram dose and that was not so. The Panel considered that the claim was misleading and inconsistent with the marketing authorization and a breach of the Code was ruled. Upon appeal by 3M Health Care, the Appeal Board considered that the claim at issue was not a fair reflection of the dosage requirements in the Qvar summary of product characteristics (SPC). It was inconsistent with the Qvar SPC and the Panel's ruling of a breach of the Code was upheld.

In relation to the claim that Qvar '... significantly reduces prescribing costs', Glaxo Wellcome noted that it was not stated to which products this comparison related. Through the use of such a hanging comparison, the claim implied that this reduction applied to all products previously used in these patients, regardless of dosage and presentation, which was clearly not so. Moreover, the claim was inaccurate, as there were situations in which Qvar did not reduce prescribing costs. For instance, the Qvar SPC stated that Qvar 400mcg/day was equivalent to 800 to 1000mcg/day of CFC-BDP. Glaxo Wellcome stated that the annual cost of generic CFC-BDP at the lower end of this dose range (delivered as 100mcg 4 puffs bd) was £124.67, compared with £125.63 for Qvar. Further, a generic formulation of BDP that was less expensive than the Drug Tariff price was also available and, at some doses, was less expensive than Qvar. The Panel noted that the claim at issue immediately followed a discussion of the comparative clinical benefits of Qvar versus CFC-BDP, budesonide turbo inhaler and HFA-fluticasone. The Panel did not accept that the claim at issue was a hanging comparison, it would be read in light of the preceding statements. No breach was ruled in that regard. The Panel considered that the claim at issue implied that switching from CFC-BDP, budesonide turbo inhaler or HFA-fluticasone to Qvar would significantly reduce prescribing costs in all circumstances and that was not so; the annual cost of a Beclazone 200 mcg per puff inhaler (CFC-BDP) was less than that of Qvar as acknowledged by 3M Health Care. There would be some patients (those on high doses and those aged under 12) who could not be switched to

Qvar. The Panel queried whether all the differences in cost would be seen as being significant. The claim was misleading and a breach of the Code was ruled. Upon appeal by 3M Health Care, the Appeal Board noted that only one of four Beclazone brands, Beclazone 200mcg, was less expensive than Qvar and further noted the submission of the 3M Health Care representatives that this product had a very small market share. The Appeal Board considered that in these circumstances it was not unreasonable to claim that a step over to Qvar would reduce prescribing costs. In relation to whether the reduction in prescribing costs was significant, the Appeal Board noted the submission that significant savings were possible with appropriate switches to Qvar at both primary care trust and national level. The Appeal Board noted that the claim was a very definite statement that the use of Qvar would significantly reduce prescribing costs and queried whether a reader would understand what was meant by the term 'significantly'. It also noted that not all patients could be switched to Qvar. On balance the Appeal Board considered that the claim was misleading and upheld the Panel's ruling of a breach of the Code.

The envelope for another Qvar mailing bore the words 'How to get to far away places' with a drawing of an aeroplane flying over pyramids, but did not carry any wording or logo to inform the recipient that the mailing had been sent by a pharmaceutical company. Glaxo Wellcome alleged that the envelope was disguised. The Panel considered that its earlier ruling above was relevant here. The envelope gave the impression that it contained promotional material relating to holiday travel and that was not so. The envelope thus constituted disguised promotion of a medicine and a breach of the Code was ruled.

Glaxo Wellcome stated that the claim that Qvar 'significantly reduces the cost of prescribing, even compared with generic CFC-BDP' was similar to that discussed above and was inaccurate as there were situations in which Qvar did not reduce prescribing costs compared to generic CFC-BDP. The Panel considered that its earlier ruling applied, the claim was misleading and a breach of the Code was ruled. Upon appeal by 3M Health Care, the Appeal Board noted that there were differences between the claim at issue 'Not to mention one that significantly reduces the cost of prescribing, even compared with generic CFC-BDP' and its context to that considered above 'And if that weren't enough, a step over to Qvar also significantly reduces prescribing costs'. The present claim emphasised the cost of Qvar compared to generic CFC-BDP. The claim considered above appeared on the same page as a cost comparison chart depicting the annual cost of a number of treatments (including generic CFC-BDP). The Appeal Board considered that in the circumstances the claim at issue was not misleading. No breach of the Code was ruled.

Under the subheading 'Qvar gets to far away places' it was suggested that Qvar was superior to CFC-BDP based on the results of a study which measured the mycobacterial lipoglycan stimulated release of

tumour necrosis factor- α (TNF- α) from alveolar macrophages, obtained from the terminal airways and alveoli of healthy volunteers who had received either Qvar or an equal microgram dose of CFC-BDP. No evidence had been supplied to suggest that reduction in alveolar macrophage TNF- α production under such conditions resulted in any clinically relevant improvements in asthma control with Qvar compared with CFC-BDP. Glaxo Wellcome alleged that the claim had no clinical significance. The Panel noted that a discreet section of the promotional item discussed the study. It was stated that the study was in healthy volunteers and concluded 'While Qvar exerted a significant effect upon the alveolar macrophages, the same dose of CFC-BDP had no such effect. This suggests that, unlike CFC-BDP, Qvar is capable of delivering bioactive drug to the terminal airways and alveoli'. The Panel noted that it was clearly stated that the study was in healthy volunteers and fairly reflected the findings of the study. Although the study used an *in vitro* test its findings were of some relevance to the clinical situation. The Panel did not consider, however, that the claim suggested clinical superiority for Qvar versus CFC-BDP and no breach of the Code was ruled.

In a further promotional item, the claim 'Qvar can offer quicker improvement in symptom control and better improvement in lung function compared with HFA-fluticasone' appeared above two graphs; the first depicted the mean change from baseline in the percentage of patients free from daily asthma symptoms with Qvar 800mcg or HFA-fluticasone 1000mcg, the second graph depicted the mean change from baseline in morning peak expiratory flow (PEF) (L/min) with Qvar 800mcg or HFA-fluticasone 1000mcg. Glaxo Wellcome stated that the item repeated a claim of improved lung function compared with HFA-fluticasone. Glaxo Wellcome had advised the Authority in detail of its concerns in relation to this claim in an earlier complaint (Case AUTH/1063/8/00). In the present item, the claim had now been presented graphically in such a manner as to emphasise a clinically non-significant difference. Glaxo Wellcome alleged that this claim of improved lung function versus fluticasone was in breach of the Code on the grounds of a lack of a sound statistical basis for the claim and of being a misleading representation of the clinical significance of the findings. The Panel noted that the earlier case concerned, *inter alia*, the claim 'In symptomatic patients Qvar (800mcg/day) can significantly improve clinical outcomes over HFA-fluticasone (1000mcg/day) ...' which appeared in a journal advertisement. It was alleged that the claim lacked a sound statistical basis and was a misleading representation of the clinical significance of the findings. The Panel did not consider that the claim was a fair reflection of the data and a breach of the Code had been ruled. Turning to the case before it, the Panel noted that there were differences from the earlier case. The data was depicted graphically beneath the claim '... better improvement in lung function compared with HFA-fluticasone'. Nonetheless the Panel considered that its ruling in the previous case would apply here. A breach of the

Code was ruled. Upon appeal by 3M Health Care, the Appeal Board noted that the material presently at issue had been withdrawn by 3M Health Care as part of its undertaking in the previous case. This was in line with the requirement that companies were obliged to withdraw all materials ruled in breach and any similar material. The current complaint had been made by Glaxo Wellcome before that company had been informed by the Authority of the outcome of the previous case. The Appeal Board considered that the present claim was different to that at issue in Case AUTH/1063/8/00. Nonetheless the ruling in it applied here. The Appeal Board upheld the Panel's ruling of a breach of the Code.

Glaxo Wellcome stated that the claim was repeated that Qvar 'significantly reduces prescribing costs', this time in relation to fluticasone. However, Qvar could not be prescribed to all patients who received fluticasone (ie children less than 12 years of age and adults who were not controlled on BDP or budesonide dosages in excess of 800mcg/day). Therefore this was an all-embracing and exaggerated claim. The Panel noted that its rulings above had some relevance. The claim now at issue was a specific claim that Qvar significantly reduced prescribing costs compared with fluticasone. The Panel considered that as there were some patients on fluticasone who could not be switched to Qvar the claim was all-embracing and exaggerated and a breach of the Code was ruled. Upon appeal by 3M Health Care, the Appeal Board considered that the material at issue was different to that at issue above; there was no mention of switching to Qvar or stepping over to Qvar. The previous allegation made no reference to the fact that Qvar was not suitable for some patient groups. The Appeal Board considered that Qvar would significantly reduce prescribing costs in appropriate patients compared with fluticasone. The claim was not all-embracing and exaggerated and no breach of the Code was ruled.

A breach of the Code was ruled because the item was more than four pages long but bore no reference as to where the prescribing information could be found.

Glaxo Wellcome stated that the claim 'significantly improving clinical outcomes' (on the inside of the back cover) referred to a footnote 'Compared with fluticasone, budesonide and beclomethasone'. This was referenced to three review papers. Fairfax reviewed two studies comparing Qvar to fluticasone; an open-study of Qvar 800mcg/day and fluticasone 1000mcg/day over 8 weeks; and a 6-week, double-blind study comparing Qvar 400mcg/day to fluticasone 400mcg/day. Glaxo Wellcome stated that the balance of evidence suggested that Qvar possessed similar efficacy to HFA-fluticasone, rather than superiority. Furthermore, with regard to 'significantly improving clinical outcomes' compared with beclomethasone, the only claim for significant improvement was in relation to adverse events 'considered probably or possibly related to treatment' (11% versus 16%, $p=0.012$) and 'inhalation-route adverse events' (8% versus 12%,

$p=0.042$). This claim was derived from a review by Thompson *et al* (1998) in which the results of five studies were combined. It was alleged that this claim was exaggerated and all-embracing. The Panel noted that the review by Fairfax concluded that at low doses 400mcg daily fluticasone and Qvar appeared to be equally effective. In addition, at higher doses Qvar (800mcg daily) appeared to be as effective as fluticasone 1000mcg daily. It was further stated that 'The choice between these two inhaled steroids should be based on factors other than efficacy in controlling asthma'. The Panel considered the claim 'Significantly improving clinical outcomes' with reference to fluticasone was exaggerated and all-embracing as alleged and a breach of the Code was ruled. With regard to the claim concerning beclomethasone, the Panel noted the parties' submissions regarding the review of adverse event data by Thompson *et al* and the dose response study by Busse *et al*. The Panel considered that the claim was unqualified; it overstated the totality of the data and was exaggerated in this regard. A breach of the Code was ruled. Upon appeal by 3M Health Care, the Appeal Board considered that its comments above applied to the claim 'Significantly improving clinical outcomes' with reference to fluticasone. The claim was not exactly the same as that previously ruled in breach. It was exaggerated and all-embracing. The Appeal Board upheld the Panel's ruling of a breach of the Code. With reference to beclomethasone, the Appeal Board noted the additional data submitted, Ayres *et al* (2000) and Data on file, and considered that the balance of the evidence supported the claim at issue. The Appeal Board ruled no breach of the Code.

A sealed Airomir mailing featured the phrase '50% can' on the front and '50% can't' on the back. Upon removal of three detachable strips along the outside edge of the mailing it could be opened up to reveal two pages of promotional material. Glaxo Wellcome stated that the outer sides of the mailing did not carry any wording or logo to inform the recipient that it had been sent by a pharmaceutical company, so the phrases '50% can' and '50% can't' induced the recipient to open the mailing without any possible knowledge of its content. This was an attempt to disguise the fact that the mailing was a promotional piece for a pharmaceutical product. The Panel considered that whilst the principles set out above were relevant here, the impression created by the mailing now at issue was different. The design and text on the mailing did create the impression that it contained promotional material. The Panel noted that the envelopes considered above created the impression that they contained promotional material for a specific item such as chicken soup or holiday travel rather than promotional material for medicines. The Panel did not accept that the envelope now at issue created such an expectation in the eyes of the recipient; it thus did not constitute disguised promotion of a medicine. No breach of the Code was ruled.

Glaxo Wellcome was concerned that text on the inside of the mailing stated that pressurised metered dose inhalers (pMDIs) showed little or no efficacy in

a large proportion of patients, a claim that was referenced to a study by Newman *et al* (1991), which actually cited another paper. In fact, the primary aim of the Newman study was to examine the lung deposition of ⁹⁹Tc-labelled salbutamol via pMDI and Autohaler in patients with respectively good and poor pMDI technique. Lung function measures showed some degree of improvement in all arms of the study, and no conclusions regarding lack of efficacy could be drawn, as a placebo arm was not included. Glaxo Wellcome alleged that the claim of inadequate efficacy with pMDIs was inaccurate. The Panel noted that the claim at issue was preceded by 'Can he? Can she? Can you? Co-ordinate a standard MDI, that is. Maybe you've never tried. But if you have had a go and failed you are certainly not alone. It has been estimated that as many as half of adults with asthma and an even greater proportion of children derive little benefit from their pMDIs because of inefficient inhaler technique'. The Panel noted that the claim at issue made it clear that it was an estimation. It did not state or imply that pMDIs showed no efficacy, as stated by Glaxo Wellcome. On balance the Panel considered it was a fair reflection of the data in patients with poor inhaler co-ordination and was not misleading in this regard. No breach of the Code was ruled.

Glaxo Wellcome stated that the text also included the claim that 'patients may not be much better off with a dry powder inhaler', because of inability to generate an adequate inspiratory flow rate, then went on to note that the Airomir Autohaler worked with an inspiratory flow rate of 30L/min. However, the text ignored the fact that the Accuhaler [Glaxo Wellcome's device] was a dry powder inhaler that also worked with an inspiratory flow rate of 30L/min. Omission of this fact misled by implying that all dry powder inhalers required inspiratory flow rates higher than 30L/min. Indeed the manufacturer of the Clickhaler device claimed that an inspiratory flow rate of only 20L/min was sufficient for satisfactory use of that device. In the Panel's view the statement, together with the subsequent claim for Airomir Autohaler, implied that all dry powder inhalers required an inspiratory flow rate of more than 30L/min to work. The Panel noted that although Johnson *et al* had stated that, to gain optimum effect from a turbo inhaler, an inspiratory flow rate of greater than 60L/min was required, there were other types of dry powder device which did not require such an inspiratory flow rate. The Panel noted Glaxo Wellcome's submission that the Accuhaler and the Clickhaler worked with inspiratory flow rates of 30L/min or less. The Panel considered that the claim was misleading and a breach of the Code was ruled.

The envelope for an Airomir mailing displayed the words 'Take a look inside', but did not carry any wording or logo to inform the recipient that this mailing had been sent by a pharmaceutical company. Glaxo Wellcome stated that this disguised the fact that the mailing was a promotional piece for a medicine. The Panel considered that the envelope did create the impression that it contained promotional material and no breach of the Code was ruled.

Glaxo Wellcome UK Limited complained about a number of promotional items relating to Qvar (CFC-free beclomethasone, (HFA-BDP)) and Airomir (CFC-free salbutamol) issued by 3M Health Care Limited.

A Qvar mailing (ref 0700/QV/004/033)

The A4 mailing consisted of the envelope and a four page leaflet to which was attached a sachet of chicken cup soup.

A1 Wording on envelope

COMPLAINT

Glaxo Wellcome stated that the envelope displayed the words 'Chicken soup enclosed', but did not carry any wording or logo to inform the recipient that the mailing had been sent by a pharmaceutical company. Thus, sponsorship of this item by 3M Health Care had not been declared and this, combined with the prominent reference to the inclusion of free foodstuffs, disguised the fact that the mailing was a promotional piece for a pharmaceutical product. Therefore, Glaxo Wellcome alleged that the envelope was in breach of Clause 10.1 of the Code.

RESPONSE

3M Health Care noted that Clause 10.1 of the Code and its supplementary information stipulated that envelopes must not be used for the dispatch of promotional material if they bore words implying that the contents were non-promotional. The envelopes 3M Health Care had used did not in any way set out to disguise the items as personal communications or imply that the contents were non-promotional. The envelope design and appearance were chosen appropriately and would have been difficult to mistake for a non-promotional item. 3M Health Care believed that a reasonable health professional would not perceive the envelope used to be in the guise of a personal communication or disguised as bearing contents relating to information on safety or other similar professional medical communication. It submitted that the material met the requirements of Clause 10.1.

PANEL RULING

The Panel noted that the envelope at issue was white with a grey border and a pre-paid postage stamp in the top right hand corner. The text 'Chicken soup enclosed see inside for directions' appeared at the bottom of the envelope above an address to which the mailing should be returned in the event of non delivery. The envelope featured neither a company name nor other text or design to indicate that the material originated from a pharmaceutical company or was otherwise related to the promotion of a medicine.

The Panel noted that the term promotion was defined in Clause 1.2 as any activity undertaken by a pharmaceutical company, or with its authority, which promoted the prescription, sale, supply or administration of its medicines. The supplementary

information to Clause 10.1 stated, *inter alia*, that 'Envelopes must not be used for the dispatch of promotional material if they bear words implying that the contents are non-promotional, for example that the contents provide information relating to safety'. The Panel accepted that the text created the impression that the envelope contained promotional material, but promotional material for chicken soup not a medicine. A recipient would not expect the envelope to contain material relating to the promotion of a medicine. The envelope thus constituted disguised promotion of a medicine. A breach of Clause 10.1 of the Code was ruled.

A2 Gift of chicken soup

COMPLAINT

Glaxo Wellcome noted that a sachet of chicken soup was attached to the front cover of the leaflet. The wording of the leaflet stated that Maimonides, a twelfth century physician, recommended chicken soup for patients with asthma. While the general tone of the item might be appropriate for a general commercial mailing, Glaxo Wellcome did not consider that it was of a suitable standard for promotion to healthcare professionals (for example the statement in the leaflet that: 'Were Maimonides alive today, he would surely have added Qvar to his asthma armamentarium'). As it was clear that the gift of chicken soup had no relevance to the present-day practice of medicine, Glaxo Wellcome alleged a breach Clause 18.2 of the Code.

RESPONSE

3M Health Care stated that it hoped that the provision of a single sachet of insignificant monetary value that provided some relief from a busy day for a health professional was not seen as acting against the principle of Clause 18 of the Code. Indeed, many other companies, including Glaxo Wellcome, provided gifts such as mugs bearing logos for a similar purpose. In addition a recent article (Rennard *et al*, 2000) had reported on the anti-inflammatory effect of chicken soup and this area might therefore be of increasing relevance to health professionals. 3M Health Care concluded that the chicken soup sachet was an appropriate gift in this particular case to raise awareness of how treatment for asthma had evolved.

As the sachet of chicken soup distributed to members of the health profession was both inexpensive and relevant in this instance to the practice of their profession, 3M Health Care did not agree that it was in breach of Clause 18.2 of the Code.

PANEL RULING

The sachet was affixed to the front page of the leaflet on top of a cartoon outline of a chicken. The heading read 'So what has chicken soup got to do with asthma ...'. The strapline read 'Make a cup, sit down and find out'. Page 2 introduced a twelfth century physician, Moses Maimonides, who recommended chicken soup as a specific remedy. It was stated that '... where the compassionate physician of the twelfth century hoped for the best from chicken soup his

counterparts today can use Qvar'. A recipe for chicken soup appeared on page 3.

The Panel noted that Rennard *et al* (2000) was an *in vitro* study which tested the ability of traditional chicken soup to inhibit neutrophil migration. The study found that chicken soup statistically significantly inhibited neutrophil migration and did so in a concentration dependent manner. All of the vegetables present in the soup and the chicken individually had inhibitory activity. The study authors stated that whether clinical benefits would be obtained with the chicken soup remained untested.

The Panel noted that Clause 18.2 required gifts in the form of promotional aids and prizes to be inexpensive and relevant to the practice of the profession or employment. The Panel noted that 3M Health Care had confirmed the cost to the company of each sachet as 8 pence plus VAT. In the Panel's view the cost to the company of each sachet was negligible. The sachet of chicken soup was relevant to the general theme of the material. The Panel also noted the submission that the gift would raise awareness of how treatment for asthma had evolved. The Panel considered that in the circumstances of this particular case, as the inherent value of the item was negligible, and that there was some, albeit limited, relevance to the practice of medicine, it was not unacceptable in relation to Clause 18.2 of the Code. There was therefore no breach of Clause 18.1 and the Panel ruled accordingly.

A3 Claim 'Well-validated radiolabelling techniques have demonstrated the superiority of Qvar over conventional beclomethasone (CFC-BDP) and CFC-fluticasone inhalers when it comes to delivering drug to the lungs'

COMPLAINT

Glaxo Wellcome stated that the claim clearly implied clinical superiority based on deposition data. However, these data were obtained in healthy volunteers and no evidence had been supplied to suggest that this increase in lung deposition resulted in any proportionate and clinically relevant improvements in asthma control with Qvar compared with CFC-fluticasone. Therefore, Glaxo Wellcome alleged that the claim was misleading and had no clinical significance, in breach of Clause 7.2 of the Code.

RESPONSE

3M Health Care stated that the text of the leaflet very clearly specified that the comparisons with CFC-beclomethasone and fluticasone related to the amount of drug delivered to the lungs. The formulation of Qvar had resulted in a solution with a reduced drug particle mean mass aerodynamic diameter. This had demonstrable implications for drug deposition in the lungs and drug delivery to the periphery of the lung in validated studies (Leach *et al*, 2000). This was an important issue in the area of inhaled respiratory products and inhalation drug delivery and one of interest to health professionals. The deposition data for Qvar when compared to CFC-beclomethasone had already been the subject of a complaint by Glaxo

Wellcome when no breach of the Code was found (Case AUTH/789/11/98). In that case the Panel's view was that the use of human volunteer data where it was almost identical to the clinical data was not necessarily misleading.

The claim in question did not claim or imply any clinical superiority based on deposition data as alleged. 3M Health Care had ensured that where claims for clinical efficacy had been made for Qvar, they had been substantiated by clinically relevant data and 3M Health Care therefore disagreed that there was a breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that the claim at issue was part of a block of text and immediately preceded a discussion of lung deposition in symptomatic patients, and comparative clinical claims regarding adverse events, early symptom control and lung function. The Panel considered that the claim would not be read in isolation but in the context of the item as a whole; the Panel noted that it immediately preceded discussion of clinical issues.

The Panel noted that the claim was referenced to Leach *et al* (2000), a poster, which was a comparison of the radio-labelled deposition of CFC-fluticasone, CFC-beclomethasone and CFC-free beclomethasone (Qvar) using metered dose inhalers in healthy subjects. The study concluded that lung deposition was highest for Qvar (53%) compared with fluticasone (13%) and beclomethasone (4%). Further, Qvar deposited drug evenly throughout the lungs.

The Panel also noted that studies in healthy volunteers and asthmatic patients (Leach *et al* 1997 and *ibid* 1996) confirmed that the formulation of Qvar extrafine aerosol provided greater lung and less oropharyngeal deposition than CFC-BDP (Leach 1998).

The Panel noted that 3M Health Care referred to a previous case, Case AUTH/789/11/98, which concerned the promotion of Qvar. In that case data had been used which compared CFC-BDP with Qvar; no data regarding CFC-fluticasone was used. In relation to four promotional items it was alleged that the data quoted in support of the message of increased deposition of CFC-free BDP compared with CFC-BDP, was drawn from a healthy volunteer study but it was not labelled to make it clear this was so. In the Panel's view the use of healthy volunteer data where it was almost identical to clinical data was not necessarily misleading. It was, however, assumed that data in promotional material referred to patients unless otherwise indicated and the absence of such labelling meant that the materials were misleading. A breach of Clause 7.2 was ruled. These rulings had been accepted by 3M Health Care in relation to a 'Dear Doctor' letter and a promotional slide. Upon appeal by 3M Health Care in relation to a product summary and patient information leaflet, the Appeal Board noted that additional data had been supplied and considered that given that data in patients and healthy volunteers was comparable it was not unacceptable to present healthy volunteer data and the failure to label it as such did not make it misleading. No breach of Clause 7.2 was ruled.

Turning to the present case the Panel noted that the claim now at issue differed from that in Case AUTH/789/11/98 in that it referred to CFC-fluticasone. Whilst it was referenced to data in healthy volunteers, there was some comparable data in patients available to substantiate the claim with regard to CFC-BDP. No such data had been submitted with reference to CFC-fluticasone. On balance the Panel considered the claim misleading as alleged. A breach of Clause 7.2 was ruled.

APPEAL BY 3M HEALTH CARE

3M Health Care stated that the approach used in the promotional mailing took the reader through a story line, which was divided into distinct paragraphs. The first paragraph [the claim in question] emphasised the impressive lung deposition seen with Qvar. The latter paragraphs referred to the comparative clinical data available and finally addressed potential cost savings. The claim in question was specific in reporting the data on lung deposition and drug delivery to the lungs for Qvar, CFC-beclomethasone and CFC-fluticasone. It made no clinical claims based on deposition. The claim was factually accurate, notwithstanding the use of data from a study on healthy volunteers. It accurately reflected the findings from the Leach *et al* (2000) study, which was a direct comparison of the deposition characteristics of CFC-beclomethasone, Qvar and CFC-fluticasone. The paragraph qualified that the claim for Qvar against the comparator products related specifically to the issue of drug delivery to the lungs. With regard to the fact that the study was conducted in healthy volunteers, 3M Health Care contended that this might actually overstate the deposition for CFC-fluticasone. Studies by Glaxo Wellcome (Daley-Yates *et al*, 2000) had concluded that the lung deposition of fluticasone in patients with asthma was reduced when compared to that in healthy volunteers. As noted by the Panel, the deposition for Qvar was comparable between healthy volunteers and patients with asthma. In using the data on fluticasone deposition from a study on healthy volunteers, 3M Health Care had therefore presented the best case scenario for drug delivery to lungs for the Glaxo Wellcome product.

The Panel then appeared to have included the subsequent paragraph [claim] within this part of the complaint. 3M Health Care noted that this subsequent claim was not the subject of the Glaxo complaint, which was specifically related to the claim in question. As this claim was factually accurate and supported by a reference (Leach *et al*, 2000), 3M Health Care appealed that, as a claim for superior lung deposition, it was not in breach of the Code. The subsequent claim was the subject of A4 below and should, in 3M Health Care's view, be considered separately.

APPEAL BOARD RULING

The Appeal Board noted 3M Health Care's submission that the mailing took the reader through a story line which was divided into distinct paragraphs or claims. The Appeal Board did not consider that each claim including that at issue would be considered by the reader independently; but would be considered in light of the document as a whole.

The Appeal Board noted that there was some comparable clinical data available in patients to substantiate the claim with reference to CFC-BDP. The data for fluticasone was pharmacokinetic data on ten patients and suggested that the lower systemic exposure to fluticasone in asthmatics, compared to healthy volunteers, was due to reduced pulmonary deposition. There was no lung deposition data for fluticasone in patients to support that seen in healthy volunteers. The Appeal Board noted 3M Health Care's submission that by using data on fluticasone deposition from a study on healthy volunteers it had presented the best case scenario for drug delivery to the lungs for fluticasone. Nonetheless the Appeal Board considered the claim misleading. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful.

A4 Claim '...when a patient on CFC-BDP or budesonide is symptomatic ...' a doctor '... can simply step over to Qvar without increasing the dose' and this '... can significantly improve clinical outcomes for your patients

COMPLAINT

Glaxo Wellcome alleged that this all-embracing claim suggested that all patients symptomatic on CFC-BDP or budesonide could be transferred to Qvar, at the same microgram dose. However, this was not so, as there were patient groups for whom Qvar was not suitable. Specifically, this would include all patients under 12 years of age and any patient symptomatic on CFC-BDP or budesonide at a dose in excess of 800mcg/day. As the text qualified neither the age of the patients who could be transferred nor their dose of CFC-BDP or budesonide, it would not be unreasonable for the prescriber to assume that all patients who were symptomatic on CFC-BDP or budesonide might be transferred to Qvar. Therefore, this claim encouraged use outside the terms of the marketing authorization and a breach of Clause 3.2 of the Code was alleged.

RESPONSE

3M Health Care noted that the Qvar summary of product characteristics (SPC) provided guidance on transferring patients with poorly controlled asthma from a CFC-containing inhaler and recommended that initially a 100mcg metered dose of Qvar should be substituted for 100mcg of CFC-BDP or budesonide. The claim for Qvar in the text, which stated that patients who were symptomatic on CFC-BDP or budesonide could be stepped over to Qvar without increasing the dose, was in keeping with this recommendation and did not encourage use outside the terms of the marketing authorization.

3M Health Care submitted an advertisement for Seretide by Glaxo Wellcome from a recent edition of the BMJ. This product was not indicated for use in some specific age groups, but the text did not qualify the age of patients. It was 3M Health Care's contention that the prescribing information provided the information on posology needed by practitioners.

The prescribing information on Qvar provided with the item clearly specified that the maximum recommended dose was 800mcg per day and that there were no definitive dosage data for children under 12 years age. Glaxo Wellcome had clearly chosen to take the paragraph from the text out of context. 3M Health Care contended that a qualified practitioner would not reasonably misinterpret the claim and would also be expected to refer to the prescribing information or the SPC if he/she were unfamiliar with the use of Qvar.

3M Health Care disagreed that the claim encouraged use outside the terms of the marketing authorization or that it breached Clause 3.2 of the Code and added that the company would never encourage the use of any product outside of its marketing authorization.

PANEL RULING

The Panel noted that Section 4.2 of the Qvar SPC subheaded 'Transferring patients to Qvar from a CFC-containing inhaler' detailed a two step transfer approach. A dosage conversion table was provided. With reference to dosing in poorly controlled (symptomatic) patients with asthma it was stated that such patients could 'be switched from CFC-containing beclomethasone dipropionate products to Qvar at the same microgram for microgram dose up to 800 micrograms daily. Comparative clinical trials have demonstrated that asthma patients achieve equivalent pulmonary function and control of symptoms with Qvar at lower daily doses than with CFC-containing beclomethasone dipropionate products'. The maximum recommended dose was 800 micrograms per day in divided doses. It was further stated that 'There are no data to date on Qvar in children hence no definitive dosage recommendations can be made'. The prescribing information on the item at issue stated that 'No definitive dosage data are available for children under 12 years'.

The Panel noted that there were patient groups for whom Qvar was not suitable such as symptomatic patients requiring more than 800mcg/day and children under 12 years. The claim gave the impression that all patients symptomatic on CFC-BDP or budesonide could be simply transferred to Qvar at the same microgram dose and that was not so. The Panel considered that the claim was misleading and was inconsistent with the marketing authorization. A breach of Clause 3.2 was ruled.

APPEAL BY 3M HEALTH CARE

3M Health Care noted that the Panel ruling stated that the claim did not specify the age of the patients, nor their dose of CFC-beclomethasone or budesonide and was misleading and inconsistent with the marketing authorization. 3M Health Care had reviewed a number of current advertisements appearing in medical journals. These included items promoting the use of Glaxo Wellcome products. The Panel was provided with an example of the latter but no comment had been made. The promotional item for the Glaxo Wellcome product, Seretide, claimed as its strap line, 'Great control patients can feel' which was no more all-encompassing than the claim in question.

3M Health Care believed that there was no more need for Glaxo Wellcome to state in its Seretide advertisement that the product was not authorized for use in children, than that for the Qvar licensing range to be stated in the text. Indeed, were such promotional items to include all the details of the SPC in the main text, the promotional message would become prohibitively confusing for health professionals. Prescribing information was clearly available in the piece and reasonable physicians would not be misled. In considering this issue the only equitable outcome for the Panel to reach must be that it was acceptable compared with the industry norms, including the complainant and 3M Health Care.

APPEAL BOARD RULING

The Appeal Board considered that the claim at issue was not a fair reflection of the dosage requirements in the Qvar SPC. It created the impression that all patients symptomatic on CFC-BDP or budesonide could be transferred to Qvar at the same microgram doses. This was inconsistent with the Qvar SPC. The Appeal Board upheld the Panel's ruling of a breach of Clause 3.2. The appeal on this point was unsuccessful.

A5 Claim that Qvar '... significantly reduces prescribing costs'

COMPLAINT

Glaxo Wellcome complained that it was not stated to which products this comparison related. Through the use of such a hanging comparison, the claim implied that this reduction applied to all products previously used in these patients, regardless of dosage and presentation, which was clearly not so. Moreover, the claim was inaccurate, as there were situations in which Qvar did not reduce prescribing costs. For instance, the Qvar SPC stated that Qvar 400mcg/day was equivalent to 800 to 1000mcg/day of CFC-BDP. The annual cost of generic CFC-BDP at the lower end of this dose range (delivered as 100mcg 4 puffs bd) was £124.67, compared with £125.63 for Qvar. Further, a generic formulation of BDP that was less expensive than the Drug Tariff price was also available and, at some doses, was less expensive than Qvar (eg Baker Norton's CFC-BDP 200mcg MDI 2 puffs bd had an annual cost of £114.46). A breach of Clause 7.2 of the Code was alleged.

RESPONSE

3M Health Care stated that Glaxo Wellcome had again selectively quoted the claim that Qvar 'significantly reduces prescribing costs' when it was clear from the text that the comparison followed the preceding paragraph as was evident in the sentence 'And if that weren't enough, a step over to Qvar also reduces prescribing costs'. The paragraph preceding this claim provided the comparator of CFC-BDP, budesonide and fluticasone with which the efficacy of Qvar had been compared, and there was no use of any hanging comparisons. Also very clearly on the same page was a graph depicting the cost of the

annual treatment of Qvar compared to the comparator inhaled steroids and detailing the devices and dose-regimes used in making the comparisons and the claim.

Glaxo Wellcome had stated that there were situations in which Qvar did not reduce prescribing costs. It had compared the annual cost of generically prescribed CFC-BDP delivered at 800mcg a day (100mcg 4 puffs bd) with Qvar but misleadingly omitted the preparation of Qvar used in the calculation. Health professionals were unlikely to use a CFC-BDP inhaler to deliver 800mcg per day as 4 puffs bd of a 100mcg preparation. Considering patient compliance, it would be more logical to use a 200mcg preparation at 2 puffs bd and to compare this with Qvar 400mcg per day (delivered as 100mcg preparation at 2 puffs bd). The comparative costs were £143.15 for generically prescribed CFC-BDP and £125.63 for Qvar (Drug Tariff, England and Wales, August 2000).

3M Health Care stated that in the unlikely event that CFC-BDP was used at 800mcg per day (delivered as 100mcg 4 puffs bd), the corresponding usage of Qvar would be 400mcg per day (delivered as 50mcg 4 puffs bd). The respective annual costs would be £124.67 as stated by Glaxo Wellcome for generic CFC-BDP and £114.90 for Qvar. In either event there was a cost of saving for Qvar.

Glaxo Wellcome had then inaccurately and misleadingly cited Baker Norton's CFC-BDP as a generic formulation. Baker Norton's CFC-BDP MDI 200mcg dose form was a branded form (Beclazone) that was not recognised on the Tariff as a generic prescription for CFC-BDP 200mcg inhaler (where the Glaxo Wellcome Becotide version was the designated reimbursable form). The annual cost of Beclazone in this scenario would be £114.46 compared with £114.90 for Qvar. However, this scenario was only pertinent if the Baker Norton product was prescribed by brand rather than as a generic prescription.

It was precisely because of the complexity of comparing costs of different permutations of medicines that 3M Health Care had followed the guidance provided in Clause 7.2 of the Code and not only compared like with like but also qualified the comparison clearly by stating the dose and delivery device used. 3M Health Care had compared the annual cost of treatment with Qvar and a range of other inhaled steroid molecules and devices to demonstrate the reduction in prescribing costs when stepping over treatment to Qvar from the other inhaled steroids. The inhaled steroid comparators used in the advertisement represented the majority of inhaled steroids in common usage for the treatment of asthma and a step over to Qvar would lead to a reduction in overall prescribing costs. Hence the claim for lower prescribing costs for Qvar was justified and not in breach of Clause 7.2 of the Code.

3M Health Care pointed out that Glaxo Wellcome had repeatedly attempted to misinterpret the claims made for Qvar by selectively quoting from the text. It had also attempted to misrepresent the comparative costs and 3M Health Care found this to be disingenuous and misleading.

PANEL RULING

The Panel noted that the claim in full read 'And if that weren't enough, a step over to Qvar also significantly reduces prescribing costs'. It had been accurately quoted by Glaxo Wellcome. 3M Health Care had inaccurately quoted the claim by the omission of the word 'significantly'. The claim at issue immediately followed a discussion of the comparative clinical benefits of Qvar versus CFC-BDP, budesonide turbo inhaler and HFA-fluticasone. The Panel did not accept that the claim at issue was a hanging comparison, it would be read in light of the preceding statements. No breach of Clause 7.2 was ruled in this regard.

In the Panel's view the claim would not be read in association with the graph comparing the annual costs of treatment with Qvar, fluticasone, budesonide and generic CFC-BDP. The cost of branded CFC-BDP had not been included in the graph. The claim at issue was separate to the graph and there was no allegation about the graph.

The Panel considered that the claim at issue implied that switching from CFC-BDP, budesonide turbo inhaler or HFA-fluticasone to Qvar would significantly reduce prescribing costs in all circumstances and that was not so; the annual cost of a Beclazone inhaler (CFC-BDP) was less than that of Qvar as acknowledged by 3M Health Care. There would be some patients (those on high doses and those aged under 12) who could not be switched to Qvar. The Panel queried whether all the differences in cost would be seen as being significant. The claim was misleading and a breach of Clause 7.2 was ruled.

APPEAL BY 3M HEALTH CARE

3M Health Care noted that the Panel ruling commented on three areas.

Firstly, the Panel stated that the annual cost of a Beclazone inhaler (a branded version of CFC-beclomethasone) was less than that of Qvar. It should be clarified that only Beclazone 200mcg was cheaper than Qvar in the appropriate dose form. Cost comparisons of Qvar 50 with Beclazone 100 and of Qvar 100 with Beclazone 250 clearly showed Qvar to be less expensive. 3M Health Care believed that this was a highly specific and disingenuous comparison by Glaxo Wellcome. The Beclazone 200 product represented only 3% of the total inhaled steroid market. The actual cost to the NHS when the product was prescribed as generic CFC-beclomethasone was as stated in the promotional item since such prescriptions were reimbursed on the Drug Tariff at the rate of the more expensive (than Qvar) Glaxo Wellcome 200mcg CFC-BDP form. The product was therefore only cheaper when it was prescribed by brand name. It should also be noted that the Beclazone 200 product was only one of 129 inhaled steroid treatment packs listed and the promotional claim for Qvar was accurate for the overwhelming majority of inhaled steroid products in the relevant dosage. The details of the cost savings were depicted in the graph so that a health professional could see clearly how these were calculated. 3M Health Care maintained that the pricing claim for Qvar was a true

reflection of the real cost of inhaled steroids in clinical practice and, as detailed in its initial response, took into account the complex issues in calculating this cost.

Secondly, the Panel commented on the issue of some groups of patients who might not be able to be prescribed Qvar and, in reply, 3M Health Care referred to the points in A4 above.

In the third and final point, the Panel queried whether all the differences in cost would be seen as significant. Asthma affected approximately 7% of the population of whom over 70% were prescribed inhaled steroids. The annual cost in England and Wales for inhaled steroids was approximately £317 million. In this context even the 7.5% cost saving seen between generic CFC-beclomethasone and Qvar could be seen as a significant amount.

3M Health Care therefore contended that the claim for significantly reducing prescribing costs compared to fluticasone, budesonide and generic CFC-beclomethasone was not misleading and did not breach Clause 7.2 of the Code. It therefore appealed against the ruling of the Panel.

APPEAL BOARD RULING

The Appeal Board firstly considered whether Qvar reduced prescribing costs. The Appeal Board noted that only one of four Beclazone brands, Beclazone 200mcg, was less expensive than Qvar and further noted the submission of the company representatives that this product had a very small market share. The Appeal Board considered that in these circumstances it was not unreasonable to claim that a step over to Qvar would reduce prescribing costs. There was however no complaint about reducing costs.

In relation to whether the reduction in prescribing costs was significant, the Appeal Board noted the submission that significant savings were possible with appropriate switches to Qvar at both primary care trust and national level. The Appeal Board noted that the claim was a very definite statement that the use of Qvar would significantly reduce prescribing costs and queried whether a reader would understand what was meant by the term 'significantly'. It also noted its ruling in point A4 above that not all patients could be switched to Qvar. On balance the Appeal Board considered that the claim was misleading. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful.

B Qvar mailing (Ref 0900/QV/004/038)

The mailing consisted of an envelope and a four page leaflet.

B1 Wording on envelope

COMPLAINT

Glaxo Wellcome stated that the envelope displayed the words 'How to get to far away places' with a drawing of an aeroplane flying over pyramids, but

did not carry any wording or logo to inform the recipient that the mailing had been sent by a pharmaceutical company. Thus, sponsorship of this item by 3M Health Care had not been declared and this, combined with the reference to travel and exotic locations, disguised the fact that the mailing was a promotional piece for a pharmaceutical product. Therefore, as with the item in point A1 above, Glaxo Wellcome alleged that the envelope used to deliver this item was disguised and in breach of Clause 10.1 of the Code.

RESPONSE

Once again 3M Health Care emphasised that the envelopes it had used to deliver the leaflet did not in any way set out to disguise the items as personal communications or imply that the contents were non-promotional. The envelope design and appearance were chosen appropriately and would have been difficult to mistake for a non-promotional item. 3M Health Care believed that a reasonable health professional would not perceive the envelope used to be in the guise of personal communication or disguised as bearing contents relating to information on safety or other similar professional medical communication. It submitted that the material met the requirements of Clause 10.1.

PANEL RULING

The Panel considered that its ruling at A1 above was relevant here. The envelope gave the impression that it contained promotional material relating to holiday travel and that was not so. The envelope thus constituted disguised promotion of a medicine. A breach of Clause 10.1 was ruled.

B2 Claim ‘When a patient on CFC-BDP or budesonide is symptomatic ...’ a doctor ‘can simply step over to the same dose of Qvar’ and this ‘... can significantly improve clinical outcomes for your patients’

COMPLAINT

Glaxo Wellcome stated that as discussed above in point A4, this all-embracing claim encouraged use of Qvar outside the terms of the marketing authorization, namely in patients under the age of 12 years or symptomatic on doses of CFC-BDP or budesonide in excess of 800mcg/day. A breach of Clause 3.2 of the Code was alleged.

RESPONSE

3M Health Care noted that the Qvar SPC provided guidance on transferring patients with poorly controlled asthma from a CFC-containing inhaler and recommended that initially a 100mcg metered dose of Qvar should be substituted for 100mcg of CFC-BDP or budesonide. The claim for Qvar in the text, which stated that patients who were symptomatic on CFC-BDP or budesonide could be stepped over to Qvar without increasing the dose, was in keeping with this recommendation and did not encourage use outside the terms of the marketing authorization.

3M Health Care submitted a recent journal advertisement for Seretide. This product was not indicated for use in some specific age groups, but the text did not qualify the age of patients. It was 3M Health Care’s contention that the prescribing information provided the information on posology needed by practitioners.

The prescribing information on Qvar provided with the item clearly specified that the maximum recommended dose was 800mcg per day and that there were no definitive dosage data for children under 12 years of age. Glaxo Wellcome had clearly chosen to take the paragraph from the text out of context. 3M Health Care contended that a qualified practitioner would not reasonably misinterpret the claim and would also be expected to refer to the prescribing information of the SPC if she/she was unfamiliar with the use of Qvar.

3M Health Care disagreed that the claim encouraged use outside the terms of the marketing authorization or that it breached Clause 3.2 of the Code. 3M Health Care would never encourage the use of any product outside its marketing authorization.

PANEL RULING

The Panel considered that its ruling at point A4 above applied here. A breach of Clause 3.2 was ruled.

APPEAL BY 3M HEALTH CARE

3M Health Care stated that it appealed on the same grounds as detailed in A4 above.

APPEAL BOARD RULING

The Appeal Board considered that this point was covered by its ruling at point A4 above. The Appeal Board upheld the Panel’s ruling of a breach of Clause 3.2. The appeal on this point was unsuccessful.

B3 Claim that Qvar ‘...significantly reduces the cost of prescribing, even compared with generic CFC-BDP’

COMPLAINT

Glaxo Wellcome stated that the item made a similar claim concerning cost savings with Qvar to that discussed in point A5. It was claimed that Qvar ‘significantly reduces the cost of prescribing, even compared with generic CFC-BDP’. As highlighted in point A5, this claim was inaccurate as there were situations in which Qvar did not reduce prescribing costs compared to generic CFC-BDP. A breach of Clause 7.2 of the Code was alleged.

RESPONSE

3M Health Care noted that Glaxo Wellcome complained that the claim that Qvar ‘significantly reduces the cost of prescribing, even compared with generic CFC-BDP’ was in breach of Clause 7.2 of Code. Glaxo Wellcome had stated that there were situations in which Qvar did not reduce prescribing costs. It had compared the annual cost of generically prescribed CFC-BDP delivered at 800mcg a day

(100mcg 4 puffs bd) with Qvar but misleadingly omitted the preparation of Qvar used in the calculation. Health professionals were unlikely to use a CFC-BDP inhaler to deliver 800mcg per day as 4 puffs bd of a 100mcg preparation. Considering patient compliance, it would be more logical to use a 200mcg preparation at 2 puffs bd and to compare this with Qvar 400mcg per day (delivered as a 100mcg preparation at 2 puffs bd). The comparative costs were £143.15 for generically prescribed CFC BDP and £125.63 for Qvar (Drug Tariff, England and Wales, August 2000).

In the unlikely event that CFC-BDP was used at 800mcg per day (delivered as 100mcg 4 puffs bd), the corresponding usage of Qvar would be 400mcg per day (delivered as 50mcg 4 puffs bd). The respective annual costs would be £124.67 as stated by Glaxo Wellcome for generic CFC-BDP and £114.90 for Qvar. In either event there was a cost saving for Qvar.

Glaxo Wellcome then inaccurately and misleadingly cited Baker Norton's CFC-BDP as a generic formulation. Baker Norton's CFC-BDP MDI 200mcg dose form was a branded form (Beclazone) that was not recognised in the Tariff as a generic prescription for CFC-BDP 200mcg inhaler (where the Glaxo Wellcome Becotide version was the designated reimbursable form). The annual cost of Beclazone in this scenario would be £114.46 compared with £114.90 for Qvar. However, this scenario was only pertinent if the Baker Norton product was prescribed by brand rather than as a generic prescription.

It was precisely because of the complexity of comparing costs of different permutations of medicines that 3M Health Care had followed the guidance provided in Clause 7.2 of the Code and not only compared like with like but also qualified the comparison clearly by stating the dose and delivery device used. 3M Health Care had compared the annual costs of treatment with Qvar and a range of other inhaled steroids and devices to demonstrate the reduction in prescribing costs, when stepping over treatment to Qvar from the other inhaled steroids. The inhaled steroid comparators used in this advertisement represented the majority of inhaled steroids in common usage for the treatment of asthma and a step over to Qvar would lead to a reduction in overall prescribing costs. Hence the claim for lower prescribing costs on Qvar was justified and not in breach of Clause 7.2 of the Code.

3M Health Care pointed out that Glaxo Wellcome had recurrently attempted to misinterpret the claims made for Qvar by selectively quoting from the text and 3M Health Care found this to be very mischievous and misleading.

PANEL RULING

The Panel noted that the actual claim in the piece at issue was that Qvar could 'significantly reduce the cost of prescribing, even compared with A&H CFC-BDP'. It was not as stated by Glaxo Wellcome nor as stated by 3M Health Care. The claim was slightly different to that considered in point A5 above in that a reference was made to A&H CFC-BDP.

The claim appeared in a paragraph which referred to switching patients on CFC-BDP or budesonide to

Qvar. In the Panel's view, given the context of the claim, it would be read as switching patients on budesonide, CFC-BDP or A&H CFC-BDP to Qvar would significantly reduce the cost of prescribing. This was not so. As stated in A5 above the annual cost of Beclazone inhaler CFC-BDP was less than that of Qvar. The Panel noted that the annual cost of a Becotide inhaler (Allen and Hanburys' CFC-BDP) dosed at 800mcg/day was £143.15 (using a 200mcg inhaler). The comparable cost of Qvar (400mcg/day using a 100mcg inhaler) was £125.63 – an annual saving of £17.52. The Panel considered that its ruling at point A5 applied here. The Panel considered that the claim was misleading. A breach of Clause 7.2 was ruled.

APPEAL BY 3M HEALTH CARE

3M Health Care apologised for supplying erroneously mailing ref 0900/QV/004/038. This was a promotional piece used in the Republic of Ireland. The correct mailing that should have been sent to the Panel was 0900/QV/004/037, which was now provided. The claim in this mailing was as stated by Glaxo Wellcome and 3M Health Care that 'Qvar significantly reduces prescribing costs, even compared with generic CFC-beclomethasone'. The claim was identical to that discussed in A5. 3M Health Care appealed against the Panel ruling on the same grounds as detailed in point A5 above.

APPEAL BOARD RULING

The Appeal Board noted that there were differences between the claim at issue 'Not to mention one that significantly reduces the cost of prescribing, even compared with generic CFC-BDP' and its context to that considered at point A5 'And if that weren't enough, a step over to Qvar also significantly reduces prescribing costs'. The present claim emphasised the cost of Qvar compared to generic CFC-BDP. The claim at issue at point A5 appeared on the same page as a cost comparison chart depicting the annual cost of a number of treatments (including generic CFC-BDP).

The Appeal Board considered that in the circumstances the claim at issue (mailing Ref 0900/QV/004/037) was not misleading. No breach of Clause 7.2 was ruled. The appeal on this point was successful.

B4 Suggestion that Qvar was superior to CFC-BDP based on the results of the study by Marshall *et al*

COMPLAINT

Glaxo Wellcome stated that under the subheading 'Qvar gets to far away places' it was suggested that Qvar was superior to CFC-BDP based on the results of the study by Marshall *et al* (2000). This study used an *in vitro* test that measured the mycobacterial lipoglycan stimulated release of tumour necrosis factor- α (TNF- α) from alveolar macrophages, obtained from the terminal airways and alveoli of healthy volunteers who had received either Qvar 800mcg/day or an equal microgram dose of CFC-

BDP. These data were obtained in healthy volunteers and no evidence had been supplied to suggest that reduction in alveolar macrophage TNF- α production under such conditions resulted in any clinically relevant improvements in asthma control with Qvar compared with CFC-BDP. The claim had no clinical significance and a breach of Clause 7.2 of the Code was alleged.

RESPONSE

3M Health Care noted that Glaxo Wellcome had repeatedly attempted to take claims out of context and here it complained that a claim of clinical superiority had been made on the basis of the Marshall *et al* study. No claim of clinical superiority however was made and the fact that the study was conducted in healthy volunteers was made very clear. The text suggested that treatment with Qvar was capable of delivering bioactive drug to the terminal airways and alveoli. As stated previously, the formulation of Qvar had resulted in a solution with a reduced drug particle mean mass aerodynamic diameter and this had clear demonstrable implications for drug deposition in the lungs and drug delivery to the periphery of the lung (Leach *et al*, 1998). This was an important issue in the area of inhaled respiratory products and inhalation drug delivery and one of interest to health professionals.

As stated in point A3 above, 3M Health Care had been careful not to base any claims of clinical superiority from the data on lung deposition and had substantiated clinical claims with clinical data. 3M Health Care therefore disagreed that the claim was in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that a discreet section of the promotional item discussed Marshall *et al*. It was stated that the study was in healthy volunteers and concluded 'While Qvar exerted a significant effect upon the alveolar macrophages, the same dose of CFC-BDP had no such effect. This suggests that, unlike CFC-BDP, Qvar is capable of delivering bioactive drug to the terminal airways and alveoli'. The Panel noted that Marshall *et al*, using an *ex vivo* alveolar macrophage model, tested the hypothesis that inhaled preparations of corticosteroids might have important anti-inflammatory effects on cells of the peripheral airway. The authors stated that the findings suggested that the '... smaller-sized particles from HFA-BDP result in greater lung distribution and greater alveolar uptake, which in turn results in a higher drug concentration at the receptor site than obtained with the larger drug particles from CFC-BDP'. It was further stated that the '... inflammatory response can be modulated by the peripheral deposition of inhaled corticosteroid *in vivo*. It was observed that inhaled corticosteroids must reach the distal airways to be effective'. The authors concluded by stating 'These findings may have important implications in the development of new immunotherapeutic agents designed to improve treatment of inflammatory pulmonary disorders'.

The Panel noted that it was clearly stated that the study was in healthy volunteers and fairly reflected

the findings of Marshall *et al*. Although Marshall *et al* was an *ex vivo* study its findings were of some relevance to the clinical situation. The Panel did not consider, however, that the claim suggested clinical superiority for Qvar versus CFC-BDP as alleged. No breach of Clause 7.2 was ruled.

C Qvar promotional item (ref 0600/QV/004/028)

The claim 'Qvar can offer quicker improvement in symptom control and better improvement in lung function compared with HFA-fluticasone' appeared above two graphs; the first depicted the mean change from baseline in the percentage of patients free from daily asthma symptoms with Qvar 800mcg or HFA-fluticasone 1000mcg at weeks 3 and 8, the second graph depicted the mean change from baseline in morning peak expiratory flow (PEF) (L/min) with Qvar 800mcg or HFA-fluticasone 1000mcg.

C1 Claim for improved lung function

COMPLAINT

Glaxo Wellcome stated that the item repeated a claim of improved lung function compared with HFA-fluticasone. Glaxo Wellcome had advised the Authority in detail of its concerns in relation to this claim in an earlier complaint (Case AUTH/1063/8/00) relating to an advertisement for Qvar (0200/QV/001/018). Within the present item, the claim had now been presented graphically, in such a manner as to emphasise a clinically non-significant difference.

As stated in its previous letter, Glaxo Wellcome alleged that this claim of improved lung function versus fluticasone was in breach of Clause 7.2 of the Code on the grounds of a lack of a sound statistical basis for the claim and of being a misleading representation of the clinical significance of the findings.

RESPONSE

3M Health Care noted that Glaxo Wellcome had pointed out that this item was prepared in July and received late August. The mailing had not been used since then. 3M Health Care was found in breach of Clause 7.2 of the Code in October with regard to claims of improved lung function compared with HFA-fluticasone. 3M Health Care had undertaken not to make this claim in the future. It was therefore surprised to see this raised as a complaint from a promotional item last used in August. Glaxo Wellcome had dated its complaint almost a month after the ruling and after 3M Health Care had informed the Authority of its undertaking not to use this claim. 3M Health Care found this inappropriate and would therefore be interested to understand the rationale for this complaint on an earlier promotional item.

3M Health Care had not made this claim since the ruling and stood by its undertaking not to use it in future.

PANEL RULING

The Panel noted that Case AUTH/1063/8/00 concerned, *inter alia*, the claim 'In symptomatic

patients Qvar (800mcg/day) can significantly improve clinical outcomes over HFA-fluticasone (1000mcg/day) ...' which appeared in a journal advertisement. It was alleged that the claim lacked a sound statistical basis and was a misleading representation of the clinical significance of the findings. The Panel did not consider that the claim was a fair reflection of the data. A breach of Clause 7.2 of the Code was ruled. This ruling was accepted by 3M Health Care which provided the Authority with the requisite form of undertaking to withdraw the advertisement at issue and similar material. In consequence of this undertaking the promotional item at issue in the present case was withdrawn; it was last used by the company in August 2000.

Turning to the case before it, the Panel noted that there were differences between the present case and Case AUTH/1063/8/00. The data was depicted graphically beneath the claim '... better improvement in lung function compared with HFA-fluticasone'. Nonetheless the Panel considered that its ruling in the previous case would apply here. A breach of Clause 7.2 of the Code was ruled.

APPEAL BY 3M HEALTH CARE

3M Health Care stated that claims made by it in comparison to fluticasone were discussed in a previous complaint (Case AUTH/1063/8/00). The essence of the claim made in the above promotional item was the same as in the previous complaint. Notwithstanding the slight difference of wording or graphical representation, it should be noted that all such claims of clinical superiority in comparison to fluticasone were withdrawn and 3M had undertaken not to use the claim again.

3M Health Care appealed on the grounds of simple equity and fairness that the Panel ruling on this occasion was tantamount to 3M Health Care being found in breach of the same offence twice. In compliance with the Panel findings in the previous complaint, all of the promotion materials with the claim of improved lung function compared to fluticasone, irrespective of the layout and use of figures, had been withdrawn. 3M Health Care hoped that this would not be repeatedly held against it and contended that having taken the remedial action of withdrawing all such materials, it could not be found guilty of the same offence again.

APPEAL BOARD RULING

The Appeal Board noted the submission from 3M Health Care. The material presently at issue had been withdrawn by 3M Health Care as part of its undertaking in the previous case, Case AUTH/1063/8/00. This was in line with the requirement that companies were obliged to withdraw all materials ruled in breach and any similar material. The Appeal Board noted that the current complaint had been made by Glaxo Wellcome before that company had been informed by the Authority of the outcome of the previous case.

The Appeal Board considered that the present claim was different to that at issue in Case AUTH/1063/8/00. Nonetheless the ruling in Case

AUTH/1063/8/00 applied here. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful.

C2 Claim Qvar 'significantly reduces prescribing costs compared to fluticasone'

COMPLAINT

Glaxo Wellcome stated that the item repeated the claim that Qvar 'significantly reduces prescribing costs', this time in relation to fluticasone. However, Qvar could not be prescribed to all patients who received fluticasone (ie. children less than 12 years of age and adults who were not controlled on BDP or budesonide dosages in excess of 800mcg/day). Therefore, this was alleged to be an all-embracing and exaggerated claim in breach of Clause 7.8 of the Code.

RESPONSE

3M Health Care stated that this complaint appeared to be identical to that in point A5 and in this instance was made specifically for the claim 'Qvar significantly reduces prescribing costs compared to fluticasone.' The basis of this comparison was detailed in graphical form and specified the molecule and device for both Qvar and fluticasone. 3M Health Care failed to see how this claim could be considered all-embracing or exaggerated. With regard to Qvar not being able to be prescribed to all patients on fluticasone, 3M Health Care repeated that the Qvar SPC provided guidance on transferring a patient to Qvar from a CFC-containing inhaler. The prescribing information provided with the item was consistent with the SPC as per Clause 4.1 of the Code.

3M Health Care again drew attention to a recent journal advertisement for Seretide. This product was not indicated for use in some specific age groups, but the text did not qualify the age of patients. It was 3M Health Care's contention that the prescribing information provided the information in posology needed by practitioners.

The prescribing information on Qvar provided with the item clearly specified that the maximum recommended dose was 800mcg per day and that there were no definitive dosage data for children under 12 years of age. Glaxo Wellcome had clearly chosen to take the paragraph from the text out of context. 3M Health Care contended that a qualified practitioner would not reasonably misinterpret the claim and would also be expected to refer to the prescribing information or the SPC if he/she was unfamiliar with the use of Qvar.

PANEL RULING

The Panel noted that its rulings at A5 had some relevance. The claim now at issue was a specific claim that Qvar significantly reduced prescribing costs compared with fluticasone. The Panel considered that as there were some patients on fluticasone who could not be switched to Qvar the claim was all-embracing and exaggerated as alleged. A breach of Clause 7.8 of the Code was ruled.

APPEAL BY 3M HEALTH CARE

3M Health Care stated that it appealed on the same grounds as stated in point A5 above. Moreover, the whole piece clearly related to adult patients. The cost graph was clearly connected with the strap line at issue. The doses were directly comparable, reflected common doses and took account of the cheapest fluticasone device-molecule combination (50mcg at 8 puffs bd, even though this was clearly an illogical regime from the clinical point of view). 3M Health Care drew attention to a reference by a consultant respiratory physician (Start-up, January 2001) which highlighted that the low cost of the 50mcg 2 puffs bd of fluticasone as claimed by Glaxo Wellcome was misleading. Despite this independent assessment, 3M Health Care used this lower start-up cost in the cost comparison. It had once again given the Glaxo Wellcome product the benefit of the best-cost calculation. The cost savings claimed in the Qvar piece above were therefore probably a conservative estimate of the true savings. 3M Health Care therefore contended that the claim was not in breach of the Code.

APPEAL BOARD RULING

The Appeal Board considered that the material at issue was different to that at issue in A5 above; there was no mention of switching to Qvar or stepping over to Qvar. The allegation in A5 made no reference to the fact that Qvar was not suitable for some patient groups. The Appeal Board considered that Qvar would significantly reduce prescribing costs in appropriate patients compared with fluticasone.

The claim was not all-embracing and exaggerated. No breach of Clause 7.8 was ruled. The appeal on this point was successful.

D Qvar promotional item (ref 0600/QV/005/005)

D1 Location of prescribing information

COMPLAINT

Glaxo Wellcome stated that this item was 8 pages long but did not contain a reference to where the prescribing information could be found. A breach of Clause 4.6 of the Code was alleged.

RESPONSE

3M Health Care stated that it accepted that the item in question was more than four pages long and while the prescribing information was provided in accordance with the Code on the back page where it would be easily found, there was no clear reference given to this effect. 3M Health Care apologised for this oversight.

PANEL RULING

The Panel noted that the prescribing information appeared on the back cover page. Clause 4.6 required printed promotional material consisting of more than four pages to include a clear reference as to where the prescribing information could be found. No such reference appeared on the item and a breach of Clause 4.6 was thus ruled.

D2 Claim 'significantly improving clinical outcomes' referring to the footnote 'Compared with fluticasone, budesonide and beclomethasone'

COMPLAINT

Glaxo Wellcome stated that the claim 'significantly improving clinical outcomes' referred to a footnote 'Compared with fluticasone, budesonide and beclomethasone'. This was referenced to three review papers.

Fairfax reviewed two studies comparing Qvar to fluticasone; an open-study of Qvar 800mcg/day and fluticasone 1000mcg/day over 8 weeks (BRON-1267); and a 6-week, double-blind study comparing Qvar 400mcg/day to fluticasone 400mcg/day. In the first study, BRON-1267, Qvar had been shown significantly to improve only one parameter in comparison with fluticasone; namely the mean change from baseline in the number of days without any daytime asthma symptoms at week 3 (but not at week 8). No significant difference was seen in the primary end point, change from baseline in mean morning PEF, based on the intent-to-treat analysis in this trial. In contrast, the second study showed a statistically significant difference in favour of fluticasone 400mcg/day over Qvar 400mcg/day: the 90% confidence interval for the difference in change from baseline in mean morning PEF between Qvar and fluticasone was -0.59 to -22.47 L/min, based on the intent-to-treat population. Whilst Glaxo Wellcome accepted that the confidence interval was wholly within the ± 25 L/min predefined limit for clinical equivalence, these results did not support 3M Health Care's contentious claim of superior lung function with Qvar over fluticasone (see also point C1). When both studies were considered, the balance of evidence suggested that Qvar possessed similar efficacy to HFA-fluticasone, rather than superiority.

Furthermore, with regard to 'significantly improving clinical outcomes' compared with beclomethasone, the only claim for significant improvement was in relation to adverse events 'considered probably or possibly related to treatment' (11% versus 16%, $p=0.012$) and 'inhalation-route adverse events' (8% versus 12%, $p=0.042$). This claim was derived from a review by Thompson *et al* (1998) in which the results of five studies were combined.

Glaxo Wellcome alleged that this claim was exaggerated and all-embracing in breach of Clause 7.8 of the Code.

RESPONSE

3M Health Care stated that with regard to the claim with HFA-fluticasone, it noted that Glaxo Wellcome now referred to a promotional item prepared in July and received mid-August 2000. As stated previously, 3M Health Care was found in breach of Clause 7.2 of the Code in October 2000 with regard to claims of improved lung function compared with HFA-fluticasone. It had undertaken not to make this claim in the future, save for the specific instances it had detailed. 3M Health Care had informed Glaxo Wellcome of this undertaking and was therefore

surprised to see this raised as a complaint about a promotional item that it received in late August 2000. Glaxo Wellcome had dated its complaint in November, almost a month after the ruling and after 3M Health Care had informed the authority and Glaxo Wellcome of its undertaking not to use this claim. 3M Health Care found this inappropriate and would therefore be interested to understand the rationale for this complaint on an earlier promotional item.

With regard to CFC-beclomethasone, the outcome for overall adverse events, considered probably or possibly related to treatment, had, as stated by Glaxo Wellcome, been shown to be lower for Qvar by Thompson *et al* (1998). The study also showed that the incidence of inhalation route adverse events was significantly lower with HFA-BDP (8%) than with CFC-BDP (12%). 3M Health Care considered safety to be an important clinical outcome and both the outcomes would justify the claim of improved clinical outcomes against CFC-beclomethasone. Furthermore, the dose-response study by Busse *et al* (1998) showed that improved asthma symptom control could be achieved by using HFA-BDP at 100mcg/d but not with CFC-BDP at same dose. 3M Health Care therefore stood by the claim and contended that it was not in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted the use of the footnote to the claim in question. It was an accepted principle under the Code that a claim could not be qualified by reference to a footnote. The Panel noted that it did not have a specific allegation in this regard but requested that the company be advised of its views.

The Panel noted that the claim at issue was referenced to Worth *et al* (2000), Thompson *et al* (1998) and Fairfax (2000).

The Panel considered the claim with reference to fluticasone. The Panel noted its comments above at point C1 with reference to Case AUTH/1063/8/00 in relation to a claim 'In symptomatic patients Qvar (800mcg/day) can significantly improve clinical outcomes over HFA-fluticasone (1000mcg/day)' which was ruled in breach of Clause 7.2 of the Code as it was not a fair reflection of the data. The Panel noted that the claim now at issue was not limited to specific doses. The Panel noted that whilst the claim at issue at point C1 above did not itself refer to specific doses it appeared immediately above a graph which compared, *inter alia*, Qvar 800mcg with fluticasone.

Turning to the allegation now before it, the Panel noted that there were differences between the present allegation, point C1 above and Case AUTH/1063/8/00. The Panel nonetheless considered that the ruling in Case AUTH/1063/8/00 had some relevance to the present allegation.

The Panel noted a review article by Fairfax (2000) which examined the relative clinical effectiveness of Qvar and fluticasone and concluded that at low doses, 400mcg daily fluticasone and Qvar appeared to be equally effective. In addition at higher doses Qvar (800mcg daily) appeared to be as effective as

fluticasone 1000mcg daily. It was further stated that 'The choice between these two inhaled steroids should be based on factors other than efficacy in controlling asthma'.

The Panel considered the claim 'Significantly improving clinical outcomes' with reference to fluticasone was exaggerated and all-embracing as alleged. A breach of Clause 7.8 was ruled.

The Panel then considered the claim with reference to beclomethasone. The Panel noted the parties' submissions regarding the review of adverse event data (Thompson *et al* 1998) and the dose response study by Busse *et al* (1998). The Panel noted that the Thompson *et al* review concluded 'Equivalent efficacy at a lower dose and equivalent safety at the same dose imply that HFA-BDP may have a more favourable risk: benefit ratio than CFC-BDP when used at recommended lower doses'. Busse *et al* concluded that increasing doses of inhaled corticosteroids led to improved lung function and asthma control. The reformulation of BDP in HFA enabled effective control at much lower doses than CFC-BDP.

With regard to beclomethasone the Panel considered that the claim was unqualified; it overstated the totality of the data and was exaggerated in this regard. A breach of Clause 7.8 was ruled.

APPEAL BY 3M HEALTH CARE

3M Health Care noted that the Panel stated that it was an accepted principle under the Code that a claim could not be qualified by reference to a footnote. 3M Health Care pointed out that this guidance was not provided in the most recent edition of the Code and it was not aware that it had been highlighted in training courses.

With reference to the claim comparing Qvar to fluticasone, 3M Health Care appealed on the same grounds as detailed in point C1 above.

With reference to the claim against CFC-beclomethasone, 3M Health Care noted that the Panel appeared to have taken into consideration only the conclusions from the two references provided in support of the claim. 3M Health Care drew attention to the highlighted areas in the references where clear differences in favour of Qvar were shown with regard to clinical outcomes. With regard to CFC-beclomethasone, the outcome for overall adverse events, considered probably or possibly related to treatment, had, as stated by Glaxo Wellcome, been shown to be significantly lower for Qvar (Thompson *et al* 1998). The study also showed that the incidence of inhalation-route adverse events was significantly lower with HFS-BDP (8%) than with CFC-BDP (12%). 3M Health Care considered safety to be an important clinical outcome and both the outcomes would justify the claim of improved clinical outcomes against CFC-BDP. Finally, this publication also stated in its final paragraph that the overall therapeutic ratio of the HFA-BDP formulation would appear to be substantially more favourable than that of the conventional CFC-BDP formulation.

The dose-response study by Busse *et al* (1998) showed that improved asthma symptom control could be

achieved by using HFA-BDP at 100mcg/day but not with CFC-beclomethasone at the same dose.

In further support for the balance of evidence, 3M Health Care drew attention to Ayres *et al* (2000) which compared the important outcome measure of asthma exacerbation in patients with asthma treated with CFC-beclomethasone or Qvar prescribed at half the dose of CFC-beclomethasone. The results showed that the number of courses of oral steroids prescribed to patients in the 12-week study was significantly higher for patients on CFC-beclomethasone. The usage of oral steroids in asthma was an important outcome measure and reflected the number of exacerbations experienced by patients with asthma. The study was a real-life study conducted in a large number of patients, with 4939 patients in the Qvar group and 979 patients in the CFC-beclomethasone group. The patients treated with CFC-beclomethasone probably had more severe asthma at baseline and this might have contributed to the greater number of exacerbations in this group. Nevertheless, studies of this magnitude were valuable in showing the important clinical differences that existed between products when used in a real life clinical situation. The conclusion also stated that a greater proportion of CFC-beclomethasone patients had serious adverse events, which was clearly an important clinical outcome.

A randomised controlled study had compared patients with stable asthma treated either with their existing treatment of CFC-beclomethasone or with half the dose of Qvar. The median percentage of symptom-free days was similar in the two treatment groups at baseline, but by the end of the study the percentage was significantly higher in the HFA-BDP group than in the CFC-BDP group ($p=0.006$). This equated to 3 symptom free days per week in the HFA-BDP group compared with 1.4 per week in the CFC-BDP group at month 12 (Data on file).

3M Health Care contended that all the above studies showed a difference in important clinical outcomes between patients randomised to CFC-beclomethasone or Qvar used at half the dose of CFC-beclomethasone. The differences consistently showed better clinical outcomes with Qvar and 3M Health Care therefore believed that the claim of improved clinical outcomes compared to CFC beclomethasone was justified.

APPEAL BOARD RULING

The Appeal Board considered that its comments in C1 above applied to the claim 'Significantly improving clinical outcomes' with reference to fluticasone. The claim was not exactly the same as that previously ruled in breach. The claim was exaggerated and all-embracing. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.8 of the Code. The appeal on this point was unsuccessful.

With reference to beclomethasone, the Appeal Board noted the additional data submitted, Ayres *et al* (2000) and Data on file, and considered that the balance of the evidence supported the claim at issue. The Appeal Board ruled no breach of Clause 7.8. The appeal on this point was successful.

E1 Aiomir mailing (ref 0600/A1/002/011)

The sealed mailing featured the phrase '50% can' on the front and '50% can't' on the back. Upon removal of three detachable strips along the outside edge of the mailing it could be opened up to reveal two pages of promotional material.

E1 Wording on mailing

COMPLAINT

Glaxo Wellcome stated that the outer sides of the mailing did not carry any wording or logo to inform the recipient that it had been sent by a pharmaceutical company, so the phrases '50% can' and '50% can't' induced the recipient to open the mailing without any possible knowledge of its content. Thus, sponsorship of this item by 3M Health Care had not been declared, which represented an attempt to disguise the fact that the mailing was a promotional piece for a pharmaceutical product. A breach of Clause 10.1 of the Code was alleged.

RESPONSE

3M Health Care noted that Clause 10.1 of the Code and the supplementary information provided stipulated that envelopes must not be used for the dispatch of promotional material if they bore words implying that the contents were non-promotional (for example, that the contents provided information relating to safety) or be sent in the guise of personal communication. The envelope used to deliver the above item did not in any way set out to disguise it as a personal communication or imply that its contents were non-promotional. The envelope's design and appearance were chosen appropriately and would have been difficult to mistake for a non-promotional item. 3M Health Care believed that a reasonable health professional would not perceive the envelope used to be in the guise of a personal communication or disguised as bearing contents relating to information on safety or other similar professional medical communication. It submitted that the material met the requirements of Clause 10.1 of the Code.

PANEL RULING

The Panel considered that whilst the principles set out at A1 and B1 were relevant here, the impression created by the mailing now at issue was different. The design and text on the mailing did create the impression that it contained promotional material. The Panel noted that the envelopes at issue in points A1 and B1 created the impression that they contained promotional material for a specific item such as chicken soup or holiday travel rather than promotional material for medicines. The Panel did not accept that the envelope at issue created such an expectation in the eyes of the recipient; it thus did not constitute disguised promotion of a medicine. No breach of Clause 10.1 was ruled.

E2 Claim that pressurised metered dose inhalers (pMDIs) showed little or no efficacy in a large proportion of patients

COMPLAINT

Glaxo Wellcome was concerned that text on the inside of the mailing stated that pressurised metered dose inhalers (pMDIs) showed little or no efficacy in a large proportion of patients, a claim that was referenced to a study by Newman *et al* (1991), which actually cited another paper. In fact, the primary aim of the Newman study was to examine the lung deposition of ⁹⁹Tc-labelled salbutamol via pMDI and Autohaler in patients with respectively good and poor pMDI technique. Lung function measures showed some degree of improvement in all arms of the study, and no conclusions regarding lack of efficacy could be drawn, as a placebo arm was not included. Glaxo Wellcome alleged that the claim of inadequate efficacy with pMDIs was inaccurate in breach of Clause 7.2 of the Code.

RESPONSE

3M Health Care stated that it was surprised that Glaxo Wellcome had complained about the claim that a pMDI showed little or no efficacy in a large number of patients as this was the exact wording used in the referenced article by Newman *et al*. Newman was recognised as a leading international authority on the use of inhalers in the treatment of asthma. 3M Health Care was further surprised at Glaxo Wellcome's interpretation of the results from the study. The study was conducted in patients with asthma and compared aerosol deposition and bronchodilator response following inhalation from the Autohaler and from a conventional metered dose inhaler in two groups of patients; those with either good or bad inhaler co-ordination. The results clearly stated that for the bad co-ordinators there was a significant reduction of the dose deposited in the lungs with their own metered dose inhaler technique. The area under the FEV1 bronchodilator response curve was significantly greater with taught metered dose inhaler and Autohaler than with 'own metered dose inhaler' for the poor co-ordinators. The authors made the point in the discussion that 'the observation of a greatly reduced bronchodilator response when the dyscoordination occurs at the end of inhalation is in agreement with the results of earlier studies'. Another publication by a leading international authority in asthma (Pedersen *et al* 1986) showed that of the 256 asthmatic children studied, in only 109 (45%) did the inhalation result in an increase in FEV1 of more than 15% (efficient technique). 3M Health Care contended that the function of a bronchodilator was to improve lung function in patients with asthma. Since this function was greatly reduced in studies on asthmatic patients, the claim was appropriate. Indeed the British Guidelines on Asthma Management (Thorax 1995) also emphasised that many patients were unable to use MDIs correctly.

3M Health Care believed therefore that the statement did not breach the principle of Clause 7.2 of the Code and that the balance of opinion on pMDI suggested that a large proportion of patients did not use the device effectively.

3M Health Care stated that it would like to highlight that Glaxo Wellcome had intentionally misquoted the statement on the inside of the mailing as stating that pMDIs showed little or no efficacy in a large proportion of patients. The statement read '... as many as half of adults with asthma and an even greater proportion of children derive little benefit from their pMDIs because of inefficient inhaler technique'. There was no suggestion that patients derived no benefit from an MDI.

PANEL RULING

The Panel noted the correct version of the claim as it appeared in the mailing. The claim at issue was preceded by 'Can he? Can she? Can you? Co-ordinate a standard MDI, that is. Maybe you've never tried. But if you have had a go and failed, you are certainly not alone. It has been estimated that as many as half of adults with asthma and an even greater proportion of children derive little benefit from their pMDIs because of inefficient inhaler technique'.

Newman *et al* stated that the metered dose inhaler was difficult to use correctly. Probably the most important error confounding the use of the MDI was failure to co-ordinate or synchronise the actuation of the inhaler with inhalation. The study compared the Autohaler with a pMDI in terms of aerosol deposition and bronchodilator response in 18 patients. In the eight patients who could not co-ordinate, the mean (SEM) percentage of the dose deposited in the lungs with their own inhaler technique (7.2%, (3.4%)) was substantially lower than those attained by the taught metered dose inhaler technique (22.8% (2.5%)) and by Autohaler (20.8% (1.7%)).

The Panel noted that this was a small study whose authors stated that the patients might not necessarily reflect the population at large. Reference was made to supporting studies by Crompton *et al* (1982) and Pederson *et al* (1986). The study authors concluded that the Autohaler should 'be a valuable alternative to dry powder inhalers and spacer devices for patients unable to use a conventional pressurised metered dose inhaler because of co-ordination difficulties'.

Pederson *et al* noted that poor results in many children indicated that too often inadequate effort was made to instruct the child or that instructors were incompetent.

The Panel noted that the claim at issue made it clear that it was an estimation. It did not state or imply that pMDIs showed no efficacy, as stated by Glaxo Wellcome. On balance the Panel considered it was a fair reflection of the data in patients with poor inhaler co-ordination and was not misleading in this regard. No breach of Clause 7.2 was ruled.

E3 Statement that '... patients may not be much better off with a dry powder inhaler ...'

This statement was the first half of the sentence which appeared as a separate paragraph immediately beneath the claim at issue in point E2 and continued 'where they may not be able to generate the optimum flow rate required for such a device'. The next paragraph began 'Happily Airomir Autohaler works with a inspiratory flow rate as low as 30L/min ...'.

COMPLAINT

Glaxo Wellcome stated that the text also included the claim that 'patients may not be much better off with a dry powder inhaler', because of inability to generate an adequate inspiratory flow rate, then went on to note that the Airomir Autohaler worked with an inspiratory flow rate of 30L/min. However, the text ignored the fact that the Accuhaler [Glaxo Wellcome's device] was a dry powder inhaler that also worked with an inspiratory flow rate of 30L/min. Omission of this fact misled by implying that all dry powder inhalers required inspiratory flow rates higher than 30L/min. Indeed the manufacturer of the Clickhaler device (Medeva Pharma Ltd) claimed that an inspiratory flow rate of only 20L/min was sufficient for satisfactory use of that device. Glaxo Wellcome alleged a breach of Clause 7.2 of the Code.

RESPONSE

3M Health Care stated that Glaxo Wellcome had repeatedly attempted to use quotes from the promotional items out of context. The item set out to convey some of the difficulties that some patients might have with some devices used to deliver inhaled asthma medication. The statement 'Your patients may not be much better off with a dry powder inhaler where they may not be able to generate the optimum flow rate required for such a device' was clearly referenced to Johnson *et al* (1996) which reported on the turbo-inhaler device. The inspiratory flow rate was clearly important for dry powder inhalers as no chemical propellants were used. The generation of an optimum inspiratory flow was needed to deagglomerate the drug particles into a respirable size in order to deliver the dose satisfactorily to the lower airways. It should be noted that the British Guidelines on Asthma Management (1995) stated that there were significant variations in drug deposition from dry powder inhalers and that inspiratory flow rates also caused variation with the same device.

3M Health Care therefore stood by its statement that some patients might not be able to generate the optimum flow rate required for such a dry powder inhaler. 3M Health Care believed that the statement was accurate and not misleading and not in breach of Clause 7.2 of the Code.

PANEL RULING

In the Panel's view the statement, together with the subsequent claim for Airomir Autohaler, implied that all dry powder inhalers required an inspiratory flow rate of more than 30L/min to work. The Panel noted that although Johnson *et al* had stated that, to gain optimum effect from a turbo inhaler, an inspiratory flow rate of greater than 60L/min was required, there

were other types of dry powder device which did not require such an inspiratory flow rate. The Panel noted Glaxo Wellcome's submission that the Accuhaler and the Clickhaler worked with inspiratory flow rates of 30L/min or less. The Panel considered that the claim was misleading. A breach of Clause 7.2 was ruled.

F Airomir mailing item (ref 0600/A1/002/012)

COMPLAINT

Glaxo Wellcome stated that the envelope displayed the words 'Take a look inside', but did not carry any wording or logo to inform the recipient that this mailing had been sent by a pharmaceutical company. Thus, sponsorship of this item by 3M Health Care had not been declared, which disguised the fact that the mailing was a promotional piece for a pharmaceutical product. Therefore, Glaxo Wellcome alleged that the envelope was in breach of Clause 10.1 of the Code.

RESPONSE

3M Health Care noted that this complaint regarding the envelope was similar to that in Point A1 and 3M Health Care repeated that the envelopes did not in any way set out to disguise the items as personal communications or imply that the contents were non-promotional. The envelope design and appearance were chosen appropriately and would have been difficult to mistake for a non-promotional item.

3M Health Care believed that a reasonable health professional would not perceive the envelope used to be in the guise of a personal communication or disguised as bearing contents relating to information on safety or other similar professional medical communication. It submitted that it had met the requirements of Clause 10.1 of the Code.

3M Health Care noted that Glaxo Wellcome had expressed concern that the use of disguised promotion by 3M Health Care was a recurring issue. 3M Health Care trusted that it had addressed this and emphasised that it was never its intention to act out of accordance with the Code.

PANEL RULING

The Panel considered that the principles set out at its ruling at point E1 applied here. No breach of Clause 10.1 of the Code was ruled.

Complaint received	1 December 2000
Case completed	5 April 2001

PHARMACEUTICAL/PRESCRIBING ADVISERS and PRESCRIBING LEAD v JANSSEN-CILAG and ORGANON LABORATORIES

Risperdal letter and tablet recognition leavepiece

Four pharmaceutical/prescribing advisers and one prescribing lead from two health authorities and a primary care group complained about a Risperdal (risperidone) letter and a tablet recognition leavepiece from Janssen-Cilag and Organon Laboratories.

The letter addressed the Committee on Safety of Medicines (CSM)'s recently announced restrictions on the prescription of the antipsychotic thioridazine, currently prescribed for over 250,000 patients in the UK. The letter stated that, within the context of mental illness, many elderly patients were treated for agitation, restlessness and anxiety with thioridazine and that the CSM had stated that the risk:benefit ratio concerning rare but serious cardiotoxicity was unfavourable in these indications and that doctors should re-evaluate these patients. The letter informed the reader that they therefore needed to make a decision regarding the therapeutic options for many patients currently receiving thioridazine. Four benefits of Risperdal therapy were then listed as stabpoints with each mention of the product name being in bold block capitals. The letter gave dosage information with regard to switching patients from thioridazine to Risperdal. The strapline 'From psychotic to cool, calm and collected' ran along the bottom edge of the letter.

The tablet recognition leavepiece was a laminated card, the front of which bore the strapline 'From psychotic to cool, calm and collected'. The claims 'Risperdal is effective in aggressive agitated elderly patients' and 'The starting dose is 0.5mg bd' appeared beneath the strapline. The bottom half of the card displayed photographs of the different presentations and formulations of Risperdal and included the claim 'A highly flexible range for the elderly'. The leavepiece was part of an earlier campaign and had not been distributed with the letters.

In Cases AUTH/1114/1/01 and AUTH/1117/1/01, the complainants stated that thioridazine was commonly used in elderly patients for agitation, restlessness and anxiety as stated in the letter. However, the letter then seemed to suggest Risperdal as a suitable alternative option. Although the letter stated that Risperdal had a well established efficacy and safety profile in patients suffering psychotic symptoms, by including this information after the sentence advising GPs to make a decision on the available options the inference was that these options included Risperdal. Risperdal was specifically licensed for psychoses including symptoms of schizophrenia; nowhere did the letter alert prescribers to the fact that it was not licensed for agitation, restlessness and anxiety in the elderly.

Cases AUTH/1116/1/01 and AUTH/1118/1/01 concerned similar allegations. The complainants referred to both the letter and the leavepiece.

In Cases AUTH/1119/1/01 and AUTH/1120/1/01, the complainant stated that the letter had been sent in the wake

of the CSM warning on thioridazine. With the restriction of this medicine doctors and psychiatrists faced a large workload reviewing patients prescribed thioridazine and assessing the need for treatment. If further medication was necessary, the vast majority looked likely to require a different medicine. Several alternatives had been suggested in local and regional bulletins and by individual clinicians and these included risperidone. However, it had been noted by these groups that risperidone was not licensed for the treatment of generalised agitation, restlessness and anxiety, nor as a sedative. These indications formed a significant proportion of the overall use of thioridazine, especially in elderly patients. The complainant noted that the letter referred to the use of thioridazine in this way, and the need for review, and then went on to promote Risperdal as an 'atypical antipsychotic with a well-established efficacy and safety profile in the elderly'. The complainant considered that the letter was wrongly promoting Risperdal for an unlicensed purpose, which it did not directly advise doctors of in the text.

The Panel noted that prior to the CSM warning thioridazine had been used to treat: schizophrenia; anxiety, agitation and restlessness in the elderly; moderate to severe psychomotor agitation; violent and dangerously impulsive behaviour; mania/hypomania; behavioural disorders and epilepsy in children. Its use was now restricted to the second line treatment of schizophrenia in adults. Prior to the CSM warning thioridazine data sheets had included a specific dosage recommendation for the treatment of 'anxiety, agitation and restlessness in the elderly: 30-100mg' as a distinct dosage recommendation from its use in patients with schizophrenia (150-600mg).

The Panel noted that Risperdal was indicated for the treatment of acute and chronic schizophrenic psychoses, and other psychotic conditions in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility and suspiciousness) and/or negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) were prominent. Risperdal also alleviated affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia. In contrast to the previous licence for thioridazine, Risperdal had no licensed non-antipsychotic use. The Panel noted that the letter described thioridazine as an antipsychotic and went on to state that within the context of mental illness many elderly patients were treated for agitation, anxiety and restlessness with thioridazine. In the Panel's view symptoms of agitation, anxiety and

restlessness might occur in schizophrenia but noted that of these only anxiety was referred to in the Risperdal SPC. The three symptoms were, however, the same symptoms that had been mentioned in previous thioridazine data sheets when referring to the (non-psychotic) elderly. In addition the Panel considered that while the term 'mental illness' would include schizophrenia it was not limited to such a specific state; not all mentally ill patients were schizophrenic.

Readers of the letter were told that, in the light of the CSM advice, they would have to make a decision regarding the therapeutic options for many patients currently receiving thioridazine. There then followed four stabpoints, each of which began with the product name Risperdal in bold block capitals. The first stabpoint described Risperdal as an atypical antipsychotic with a well-established efficacy and safety profile for elderly patients suffering from psychotic symptoms. Subsequent stabpoints stated that it was well tolerated in the elderly and easy to take and the final stabpoint gave the cost of one month's treatment.

The Panel noted that the letter stated 'If you decide to change to Risperdal after re-evaluating your patients, reduce the dose of thioridazine over one to two weeks, as advised by the CSM'. The Panel considered that this sentence was ambiguous; it could be read to mean that the CSM advised switching patients from thioridazine to Risperdal and had given specific dosage instructions for such a switch whereas the CSM advice to reduce the dose of thioridazine over one to two weeks applied to the discontinuation of the medicine generally. The letter from the CSM which had been sent to health professionals to explain the restrictions on the use of thioridazine did not suggest an alternative therapy.

The Risperdal letter had referred to the same symptoms in the elderly which, in previous thioridazine data sheets, had been used specifically in regard to a non-psychotic group of patients. In the Panel's view the letter had not drawn a clear distinction between the previously licensed non-psychotic indication for thioridazine and the licensed indications for Risperdal; the Panel considered that the strapline 'From psychotic to cool, calm and collected' was insufficient in this regard. The Panel considered that some readers would gain the misleading impression that Risperdal was licensed, and was therefore a suitable alternative to thioridazine, for the treatment of agitation, restlessness and anxiety in the non-psychotic elderly which was not so. Breaches of the Code were ruled.

The complainants in Cases AUTH/1116/1/01 and AUTH/1118/1/01 had also complained about a tablet recognition leavepiece, the content of which was very similar to that of a poster considered in a previous case, Case AUTH/1083/10/00. The heading on one side of that poster had stated 'From psychotic to cool, calm and collected'. Beneath were the claims 'Risperdal is effective in aggressive, agitated elderly patients' and 'Risperdal comes in a highly flexible range of presentations for the elderly'. The claims had been followed by a visual of the tablet

and liquid formulations of Risperdal. The Panel had considered that the general thrust of the poster was treatment of elderly patients; symptoms of aggression and agitation were mentioned. The heading referred to psychoses. The design of the poster was such that the reader's eye was drawn to the central visual and the preceding claims. The Panel had considered that whilst the claims did not refer to psychoses in the elderly they would be read in light of the heading. The Panel had considered that the poster was not misleading as alleged and no breach of the Code had been ruled.

The Panel noted that the leavepiece dealt solely with Risperdal; its purpose was to show health professionals what the various presentations and formulations of the product looked like. There was no reference to any other product. The strapline 'From psychotic to cool, calm and collected' was at the top of the leavepiece and the claim 'Risperdal is effective in aggressive, agitated elderly patients' appeared beneath it. The Panel considered that, as in Case AUTH/1083/10/00, whilst the claim did not refer to psychoses in the elderly it would be read in the light of the strapline at the top of the leavepiece. The leavepiece had not been distributed with the Risperdal letter considered above; it was part of an earlier campaign. The leavepiece did not refer to thioridazine and the treatment of 'anxiety, agitation and restlessness in the elderly'. The Panel did not consider that the leavepiece was misleading as alleged and no breach of the Code was ruled in respect of it.

Four pharmaceutical/prescribing advisers and one prescribing lead from two health authorities and one primary care group complained about a Risperdal (risperidone) letter (ref 605852) and a tablet recognition leavepiece (ref 605450) distributed by Janssen-Cilag Ltd and Organon Laboratories Ltd.

The Risperdal letter addressed the Committee on Safety of Medicine (CSM)'s recently announced significant restrictions on the prescription of thioridazine, an antipsychotic medication currently prescribed for over 250,000 patients in the UK. The letter stated that, within the context of mental illness, many elderly patients were treated for agitation, restlessness and anxiety with thioridazine and that the CSM had stated that the risk:benefit ratio concerning rare but serious cardiotoxicity was unfavourable in these indications and that doctors should re-evaluate these patients. The letter informed the reader that they therefore needed to make a decision regarding the therapeutic options for many patients currently receiving thioridazine. Four benefits of Risperdal therapy were then listed as stabpoints with each mention of the product name being in bold block capitals. The letter concluded by giving dosage information with regard to switching patients from thioridazine to Risperdal and stated that further information could be obtained from the medical information department. The strapline 'From psychotic to cool, calm and collected' ran along the bottom edge of the letter. The Risperdal product logo appeared in the bottom right hand corner.

The letter was part of a short-term mailing campaign which was sent out to primary care staff.

The tablet recognition leavepiece was a laminated card. The front of the card was headed with the Risperdal product logo beneath which was the strapline 'From psychotic to cool, calm and collected'. The claims 'Risperdal is effective in aggressive agitated elderly patients' and 'The starting dose is 0.5mg bd' appeared beneath the strapline. The bottom half of the card displayed photographs of the different presentations and formulations of Risperdal and included the claim 'A highly flexible range for the elderly'.

The leavepiece was part of an earlier campaign and had not been distributed with the letters.

Cases AUTH/1114/1/01 and AUTH/1117/1/01

The senior pharmaceutical adviser and the prescribing adviser to a health authority complained about the Risperdal letter.

COMPLAINT

The complainants noted that following the recently published CSM advice regarding thioridazine, the letter in question had been distributed to local GPs.

The complainants stated that thioridazine was commonly used in elderly patients for agitation, restlessness and anxiety as stated in the letter. However, the letter then seemed to suggest Risperdal as a suitable alternative option. Although the letter stated that Risperdal had a well established efficacy and safety profile in patients suffering psychotic symptoms, by including this information after the sentence advising GPs to make a decision on the available options the inference was that these options included Risperdal.

Risperdal was specifically licensed for psychoses including symptoms of schizophrenia; nowhere did the letter alert prescribers to the fact that it was not licensed for agitation, restlessness and anxiety in the elderly.

The complainants alleged that the letter was in breach of the Code. Clause 7.2 clearly stated that 'information, claims and comparisons must be accurate, balanced, fair, objective and unambiguous'. Also, 'they must not mislead either directly or by implication' [emphasis added].

The complainants considered that the letter needed to be withdrawn and the implication redressed in some way.

Cases AUTH/1116/1/01 and AUTH/1118/1/01

The pharmaceutical adviser and the prescribing lead to a health authority complained about the Risperdal letter and the tablet recognition leavepiece.

COMPLAINT

The complainants noted that following the recent CSM advice regarding thioridazine, the letter and tablet identification guide had been distributed to local GPs.

The complainants noted that thioridazine was commonly used in elderly patients for restlessness,

wandering and agitation as stated in the letter. However, the letter and leavepiece then seemed to suggest Risperdal as a suitable alternative option. Although the letter stated that Risperdal had a well established efficacy and safety profile in patients suffering psychotic symptoms, by including this information after the sentence advising GPs to make a decision on the available options the inference was that these options included Risperdal.

The complainants alleged that as Risperdal was specifically licensed for psychoses and symptoms of schizophrenia this letter was in breach of the Code. Clause 7.2 clearly stated that information, claims and comparisons must be accurate, balanced, fair and unambiguous and must be based on an up-to-date evaluation of all the evidence and reflect that evidence clearly. They must not mislead either directly or by implication [emphasis added].

Cases AUTH/1119/1/01 and AUTH/1120/1/01

The prescribing adviser to a primary care group complained about the Risperdal letter.

COMPLAINT

The complainant stated that the letter had been sent in the wake of the CSM warning on thioridazine. With the restriction of this medicine doctors and psychiatrists faced a large workload reviewing patients prescribed thioridazine and assessing the need for treatment. If further medication was necessary the vast majority looked likely to require a different medicine, ie not continue on thioridazine. Several alternatives had been suggested in local and regional bulletins and by individual clinicians, these included risperidone. However, it had been noted by these groups that risperidone was not licensed for the treatment of generalised agitation, restlessness and anxiety, nor as a sedative, although this use did seem to be clinically sound. These indications formed a significant proportion of the overall use of thioridazine, especially in elderly patients. The complainant noted that the letter referred to the use of thioridazine in this way, and the need for review and then went on to promote Risperdal as an 'atypical antipsychotic with a well-established efficacy and safety profile in the elderly'. The last paragraph advised doctors how to change to Risperdal after re-evaluating patients on thioridazine.

Although the second paragraph did say 'within the context of mental illness ...' (but not all mental illness was psychosis), the complainant considered that the letter was wrongly promoting Risperdal for an unlicensed purpose, which it did not directly advise doctors of in the text.

RESPONSE

Janssen-Cilag responded on behalf of both itself and Organon Laboratories.

The company firstly addressed the allegations concerning the Risperdal letter. The company noted that the letter began by conveying factual information about the CSM's decision regarding restrictions to the current licensed use of the antipsychotic thioridazine

and also drew attention to the large number of patients potentially affected. The letter then referred to the use of thioridazine in the elderly and reminded doctors of the current licensed indication in this population. The letter then further reminded doctors that they needed to re-evaluate affected patients (as advised by the CSM) and make an alternative therapeutic decision for many of them. These were statements of fact and at this juncture no mention had been made regarding a possible role for Risperdal treatment either directly or by inference.

Janssen-Cilag noted that the indication for thioridazine in the elderly was broad, symptom-based and rather non-specific. It was thus inevitable that a proportion of patients treated with thioridazine under this broad indication would in fact be suffering from a psychotic condition and would have prominent psychotic symptoms in conjunction with or actually causing their symptoms of agitation and/or restlessness.

Janssen-Cilag noted that the next section of the letter presented the case for Risperdal as one alternative therapeutic option, after re-evaluation, for those suffering psychotic symptoms as exemplified by its summary of product characteristics (SPC). The first stabpoint clearly stated the indication for psychotic symptoms and gave specific examples of the symptoms in question and was fully consistent with the Risperdal SPC which stated:

'Risperdal is indicated for the treatment of acute and chronic schizophrenic psychoses, and other psychotic conditions, in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness), and/or negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) are prominent. Risperdal also alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia'.

Janssen-Cilag stated that market research with primary care staff strongly suggested that general practitioners identified well with such descriptive symptomatology when discussing psychosis ie the language used was both relevant and tailored to its intended audience.

Janssen-Cilag stated that the sentence following the three Risperdal stabpoints was a crucial part of the letter in that it emphasised that doctors should not make the decision to use Risperdal until they had re-evaluated their patients. This re-evaluation would obviously be made in the light of the previously stated information regarding thioridazine and Risperdal and as such doctors would be fully aware that the indications for the two products were different (but not exclusive) and that Risperdal was indicated if psychotic symptoms were present. Further to this, at the foot of the letter, was the strapline: 'From Psychotic to Cool, Calm and Collected'. The strapline was prominent being in a larger font size than the other text and stylised and emboldened to draw the reader's attention. The statement itself clearly denoted the movement from a psychotic condition (diagnosis invariably required prominent positive and or negative psychotic symptoms) to a non-psychotic state (symptoms

controlled and or absent) and was therefore completely consistent with the stated SPC indication for risperidone and re-affirmed the information stated in the text regarding the indication for Risperdal. If after appropriate re-evaluation a decision was made to prescribe Risperdal then the CSM's advice on discontinuation of thioridazine was given and the licensed starting dose of Risperdal was clearly stated.

Janssen-Cilag stated that, taking the whole letter in context, the reader was first re-informed about the restrictions placed on the prescription of thioridazine by the CSM, reminded as to the current licensed indication for thioridazine in the elderly and that the CSM advised that patients be re-evaluated in the light of these restrictions. The reader was then informed of the current indication for Risperdal for psychotic symptoms and examples of psychotic symptoms were clearly stated (consistent with the current SPC). The indication for Risperdal was further reinforced by the unequivocal strapline at the foot of the letter. Given this information the reader was finally asked to re-evaluate his/her patients and decide whether it was appropriate to use Risperdal and if so, advice on substitution was given.

Janssen-Cilag did not accept that there had been a breach of Clauses 7.2 or 3.2 of the Code.

Turning to Cases AUTH/1116/1/01 and AUTH/1118/1/01, Janssen-Cilag stated that it was not clear as to exactly what the complaint about the tablet recognition leavepiece was. The company noted that this leavepiece was from an earlier campaign and was not distributed with the Risperdal letter. Janssen-Cilag stated that it assumed that the complainants considered that the leavepiece was misleading (Clause 7.2) or promoted Risperdal outside of its current indication (Clause 3.2). Janssen-Cilag referred to the ruling in Case AUTH/1083/10/00 as the arguments were almost identical.

Janssen-Cilag stated that the leavepiece was primarily designed to highlight the availability of the recently introduced 0.5mg tablet and provided a visual identification aid to help health professionals differentiate it from other tablet strengths.

At the top of the piece was the strapline 'From Psychotic to Cool, Calm and Collected'. The strapline was a prominent part of the piece being in a larger font size than the other text and stylised and emboldened to draw the reader's attention. The statement itself clearly denoted the movement from a psychotic condition (diagnosis invariably required prominent positive and/or negative psychotic symptoms) to a non-psychotic state (symptoms controlled and/or absent) and was therefore completely consistent with the SPC indication for Risperdal.

Janssen-Cilag stated that the subsequent and secondary claim regarding aggressive, agitated elderly patients had to be seen in the context of the overarching statement regarding psychosis as described above. The company noted that it immediately followed the strapline. Market research with primary care staff strongly suggested that GPs identified well with this terminology when allied to descriptions of symptomatology ie it was relevant to

its intended audience. In the SPC hostility or aggression was clearly identified as a positive symptom and the company submitted that agitation was a very common sequelae of a psychotic state such that it would frequently accompany such a condition especially in the elderly. Thus the claim that Risperdal was effective in aggressive, agitated elderly patients within the context of psychosis was both accurate and legitimate. Janssen-Cilag stated that it had specifically chosen to highlight hostility (and agitation) here in the context of a psychotic illness as this often posed the most difficult management problems in primary care and was thus of particular relevance to the intended audience.

The company did not accept that there had been a breach of Clauses 3.2 or 7.2 of the Code.

PANEL RULING

The Panel noted that prior to the CSM warning thioridazine had been used to treat schizophrenia; anxiety, agitation and restlessness in the elderly; moderate to severe psychomotor agitation; violent and dangerously impulsive behaviour; mania/hypomania; behavioural disorders and epilepsy in children. Following the CSM advice the use of thioridazine was now restricted to the second line treatment of schizophrenia in adults. The Panel noted that prior to the CSM warning thioridazine data sheets had included a specific dosage recommendation for the treatment of 'anxiety, agitation and restlessness in the elderly: 30-100mg' as a distinct dosage recommendation from its use in patients with schizophrenia (150-600mg) (ref ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1999-2000).

The Panel noted that Risperdal was indicated for the treatment of acute and chronic schizophrenic psychoses, and other psychotic conditions in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility and suspiciousness) and/or negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) were prominent. Risperdal also alleviated affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia. The Panel noted that, in contrast to the previous licence for thioridazine, Risperdal had no licensed non-antipsychotic use.

The Panel noted that the letter described thioridazine as an antipsychotic and went on to state that within the context of mental illness many elderly patients were treated for agitation, anxiety and restlessness with thioridazine. In the Panel's view symptoms of agitation, anxiety and restlessness might occur in schizophrenia but noted that of these only anxiety was referred to in the Risperdal SPC. The three symptoms were, however, the same symptoms that had been mentioned in previous thioridazine data sheets when referring to the (non-psychotic) elderly. In addition the Panel considered that while the term 'mental illness' would include schizophrenia it was not limited to such a specific state; not all mentally ill patients were schizophrenic.

Readers of the letter were told that, in the light of the CSM advice, they would have to make a decision

regarding the therapeutic options for many patients currently receiving thioridazine. There then followed four stabpoints each of which began with the product name Risperdal in bold block capitals. The first stabpoint described Risperdal as an atypical antipsychotic with a well-established efficacy and safety profile for elderly patients suffering from psychotic symptoms. Subsequent stabpoints stated that it was well tolerated in the elderly and easy to take; the final stabpoint gave the cost of one month's treatment.

The Panel noted that the letter stated 'If you decide to change to Risperdal after re-evaluating your patients, reduce the dose of thioridazine over one to two weeks, as advised by the CSM'. The Panel considered that this sentence was ambiguous; it could be read to mean that the CSM advised switching patients from thioridazine to Risperdal and had given specific dosage instructions for such a switch whereas the CSM advice to reduce the dose of thioridazine over one to two weeks applied to the discontinuation of the medicine generally. The Panel noted that the letter from the CSM which had been sent to health professionals to explain the restrictions on the use of thioridazine did not suggest an alternative therapy.

The Risperdal letter had referred to the same symptoms in the elderly which, in previous thioridazine data sheets, had been used specifically in regard to a non-psychotic group of patients. In the Panel's view the letter had not drawn a clear distinction between the previously licensed non-psychotic indication for thioridazine and the licensed indications for Risperdal; the Panel considered that the strapline 'From psychotic to cool, calm and collected' was insufficient in this regard. The Panel considered that some readers would gain the misleading impression that Risperdal was licensed, and was therefore a suitable alternative to thioridazine, for the treatment of agitation, restlessness and anxiety in the non-psychotic elderly which was not so. Breaches of Clauses 3.2 and 7.2 were ruled.

The Panel noted that the complainants in Cases AUTH/1116/1/01 and AUTH/1118/1/01 had also complained about a tablet recognition leaviepiece; the content of the leaviepiece was very similar to that of a poster considered in a previous case, Case AUTH/1083/10/00. The heading on one side of the poster had stated 'From psychotic to cool, calm and collected', the first three words being over-printed with the same words slightly offset. Beneath were the claims 'Risperdal is effective in aggressive, agitated elderly patients' and 'Risperdal comes in a highly flexible range of presentations for the elderly'. The claims had been followed by a visual of the tablet and liquid formulations of Risperdal.

In Case AUTH/1083/10/00, the Panel had considered that the general thrust of the poster was treatment of elderly patients; symptoms of aggression and agitation were mentioned. The Panel noted that the heading referred to psychoses. The Panel noted that the design of the poster was such that the reader's eye was drawn to the central visual and the preceding claims. The Panel considered that whilst the claims did not refer to psychoses in the elderly they would

be read in light of the heading. The Panel considered that the poster was not misleading as alleged. No breach of Clauses 3.2 and 7.2 had been ruled.

In the present cases, Cases AUTH/1116/1/01 and AUTH/1118/1/01, the Panel noted that the leavepiece dealt solely with Risperdal; its purpose was to show health professionals what the various presentations and formulations of the product looked like. There was no reference to any other product. The strapline 'From psychotic to cool, calm and collected' was at the top of the leavepiece and the claim 'Risperdal is effective in aggressive, agitated elderly patients' appeared beneath it. The Panel considered that, as in Case AUTH/1083/10/00, whilst the claim did not refer to psychoses in the elderly it would be read in the light of the strapline at the top of the leavepiece. The Panel noted Janssen-Cilag's submission that the leavepiece had not been distributed with the Risperdal letters considered above; it was part of an

earlier campaign. The leavepiece did not refer to thioridazine and the treatment of 'anxiety, agitation and restlessness in the elderly'. The Panel did not consider that the leavepiece was misleading as alleged. No breach of Clause 7.2 was ruled.

Complaints received

Case AUTH/1114/1/01	4 January 2001
Case AUTH/1116/1/01	8 January 2001
Case AUTH/1117/1/01	4 January 2001
Case AUTH/1118/1/01	8 January 2001
Case AUTH/1119/1/01	9 January 2001
Case AUTH/1120/1/01	9 January 2001
Cases completed	23 February 2001

CASE AUTH/1115/1/01

GLAXOSMITHKLINE v LUNDBECK

Cipramil detail aid

GlaxoSmithKline complained about a Cipramil (citalopram) detail aid produced by Lundbeck and entitled 'Cipramil Antidepressant not antipsychotic'. GlaxoSmithKline supplied Seroxit (paroxetine).

In relation to the claims 'Effective in panic disorder – a severe form of anxiety' and 'Proven efficacy in panic disorder, a severe form of anxiety', GlaxoSmithKline alleged that the inclusion of the word 'anxiety' implied that Cipramil was licensed for the treatment of anxiety states other than panic disorder which was not so. The Panel noted the difficulties in classifying and defining anxiety and panic attacks. Cipramil was licensed to treat panic disorder, a condition characterised by discreet episodes of severe anxiety; it was not licensed to treat anxiety *per se*. The Panel considered that the claims at issue were not sufficiently clear about the licensed indication of the product and a breach of the Code was ruled.

The claim 'Fewer reported adverse events than other SSRIs', referenced to Edwards and Anderson (1999), appeared as a heading above a table which favourably compared the total reports and total reactions of five classes of adverse reaction for Cipramil to those for fluvoxamine, fluoxetine, sertraline and paroxetine. The data for Cipramil appeared in a highlighted green column. GlaxoSmithKline alleged that it was misleading to use spontaneous 'yellow card' data, collected at different times, to imply a lower incidence of adverse reactions to citalopram compared with other selective serotonin re-uptake inhibitors (SSRIs). Such reporting rates were open to numerous biases as acknowledged by both the MCA and Edwards and Anderson. As the implied claim was not justified by the data presented nor supported by any comparative clinical trial data, it was misleading. The Panel noted that Edwards and Anderson considered data from a

meta-analysis of twenty short-term comparative studies, data from the CSM yellow card reports and data from the Prescription Event Monitoring System and the authors' conclusions about the advantages and disadvantages of each SSRI were based on these three sources, not yellow card reports alone. The authors noted that a disadvantage of citalopram was that 'It was comparatively new with therefore less chance of rare adverse reactions having been identified'. The Panel considered that the claim at issue and the table of data invited the reader to directly compare the number of adverse event reports received for each SSRI listed and implied that it was fair to do so. That was not so. The comparison was unfair. A breach of the Code was ruled.

The claim 'Cipramil is simple to initiate in panic disorder and does not require complex titration' appeared beneath the heading 'Simplicity in panic disorder' and above a table headed 'Cipramil v paroxetine' which compared various features of the two products. GlaxoSmithKline stated that as the only other medication mentioned on the page was paroxetine, the implication of this claim was that paroxetine, compared to citalopram, was difficult to initiate in panic disorder and required a complex titration. Neither of these implications was correct. The Panel did not accept Lundbeck's assertion that the claim was not linked to the table comparing Cipramil and paroxetine. The claim appeared immediately above the table; both the claim and the table referred to initiation of therapy. The Panel considered that the claim would be viewed as a

comparison with paroxetine. The Panel noted the summaries of product characteristics (SPC) for the two products. The Panel considered that in the context of the page on which it appeared the claim gave the misleading impression that paroxetine therapy was more difficult to initiate and required a more complex dose titration regimen than Cipramil therapy. This was not so. A breach of the Code was ruled.

The claim 'Can be taken at any time of day' appeared in the above table comparing Cipramil and paroxetine. A tick appeared in the Cipramil column and a cross in the paroxetine column; GlaxoSmithKline stated that this was incorrect. The SPC for paroxetine simply stated that it was recommended to be given in the morning. This did not mean it could not be taken at any other time of day, which was the interpretation readers of this item could reach. Indeed, GlaxoSmithKline was aware that some patients were advised by their doctor to take paroxetine in the evening. The Panel noted that the Seroxat SPC stated that 'It is recommended that 'Seroxat' be administered once daily in the morning with food'. This was a recommendation only, the SPC did not state that Seroxat must be taken in the morning and so, in the Panel's view, the administration of paroxetine at a different time of the day was not prohibited. The Panel considered that the cross in the paroxetine column, against the claim 'Can be taken at any time of the day', was not a fair reflection of the data in the Seroxat SPC. A breach of the Code was ruled.

The claim '40mg OD- for severe and recurrent depression' appeared beneath the heading 'Easy to prescribe'. GlaxoSmithKline stated that this dosage for this indication was not mentioned in the citalopram SPC. After initiation of 20mg/day in depressed patients, the SPC stated that the dose might be increased to a maximum of 60mg/day, depending on response. Thus, to state that 40mg/day was 'the' dose for severe and recurrent depression, ignoring the possibility of the need for 60mg/day was misleading. The Panel noted that a specific dosage for severe and recurrent depression was not mentioned in the Cipramil SPC. The Panel considered the claim at issue was not a fair reflection of the data in the Cipramil SPC and was misleading. Breaches of the Code were ruled.

GlaxoSmithKline stated that the 'Adverse Event' section of the prescribing information given on the detail aid mentioned the following adverse events: nausea, tremor, somnolence, dry mouth and 'withdrawal symptoms' (sic). This totalled five different adverse events, if the unspecified 'withdrawal symptoms' were counted as a single event. In contrast, the Cipramil SPC listed fifty-seven different adverse events. Clearly the prescribing information failed to adequately give '... in an abbreviated form, the substance of the relevant information in the summary of product characteristics'. The Panel noted that the 'Undesirable effects' section of the SPC and the 'Adverse Events' section of the prescribing information listed those adverse events which were most commonly associated with Cipramil and which had occurred with a greater incidence than in

placebo-treated patients. Both documents also referred to withdrawal reactions which had been reported in association with SSRIs including Cipramil. The Panel noted that the SPC then listed treatment emergent adverse events reported in clinical trials (n=2985). Fifteen events were listed as frequent (≥5-20%), thirty-four as less frequent (1- <5%) and eight as rare (<1%). None of this information was included in the prescribing information. The Panel considered that by not referring at all to treatment emergent adverse events the prescribing information, with regard to side effects, did not provide the substance of the relevant information in the SPC. A breach of the Code was ruled.

GlaxoSmithKline complained about a Cipramil (citalopram) detail aid produced by Lundbeck Limited. The detail aid was entitled 'Cipramil Antidepressant not antipsychotic' (ref 0500/CIP/525/304(412)). GlaxoSmithKline supplied Seroxat (paroxetine).

1 Claims 'Effective in panic disorder – a severe form of anxiety' and 'Proven efficacy in panic disorder, a severe form of anxiety'

The first claim appeared on page 2 (beneath a main heading 'Proven efficacy') and page 7. The second claim appeared on page 12.

COMPLAINT

GlaxoSmithKline alleged that by including the word 'anxiety' in these claims, Lundbeck was implying that Cipramil was licensed for the treatment of anxiety states other than panic disorder. This was not the case, and thus this implied claim was misleading and in breach of Clause 3.2.

RESPONSE

Lundbeck stated that a number of well respected textbook sources of psychiatric information (eg Seminars in General Adult Psychiatry Vol 1 by Stein and Wilkinson 1998; The Essentials of Postgraduate Psychiatry (3rd Edition) by Robin Murray *et al*; Companion to Psychiatric Studies (6th Edition) by Johnstone *et al*) all described panic disorder, and stated that essential features of panic disorder were recurrent attacks of very severe anxiety or panic (copies of texts were provided).

Panic attack was described as a key feature of panic disorder. The Oxford Textbook of Psychiatry (3rd Edition) by Gelder *et al* described a number of symptoms that characterised a panic attack (both somatic and/or psychological). The authors noted that important features of panic attacks were that anxiety built up quickly, the response was severe, and there was fear of a catastrophic outcome. There was certainly no doubt, especially for the unfortunate people that suffered from these attacks, that the panic attacks were a severe form of anxiety.

Such observations about panic and other psychiatric disorders, borne out by vast clinical experience, led to a pooling internationally of these experiences. This led to the development of the two classifications used

to categorise psychiatric illness; the DSMIV and ICD-10 classifications (copies of which were provided). These internationally developed classifications were well-respected worldwide and used as standards in clinical diagnosis all over the world. In both of these classifications 'panic disorder' was listed under the general heading 'Anxiety Disorders'.

It was not Lundbeck's intention to promote Cipramil usage for an unlicensed indication, as had been alleged. Lundbeck had concerns over the precise issue involving the use of the term 'anxiety' in the context of 'depression' and 'panic'. This specific matter, therefore, was addressed with the Medicines Control Agency (MCA), which reviewed materials containing this statement. All claims were acceptable as being consistent with the summary of product characteristics (SPC) and complied with The Medicines (Advertising) Regulations 1994 [SI 1994/1932, as amended]. The correspondence was provided.

Lundbeck therefore did not agree that the claim was in breach of Clause 3.2 of the Code.

PANEL RULING

The Panel noted that according to its SPC Cipramil was indicated for the treatment of depressive illness in the initial phase and as maintenance against potential relapse/recurrence. Cipramil was also indicated in the treatment of panic disorder with or without agoraphobia.

The Panel noted that the Essentials of Postgraduate Psychiatry; Neurosis and Personality Disorder stated in a section headed 'Classification of panic and situational anxiety' that there were 'a number of sources of controversy surrounding the classification and presumed mechanisms underlying panic attacks and panic disorder'. The Panel noted that ICD-10 (The International Classification of Diseases and Related Health Problems) listed the following classifications under 'Other anxiety disorder'; panic disorder [episodic paroxysmal anxiety] (excluding panic disorder with agoraphobia), generalised anxiety disorder, mixed anxiety and depressive disorder, other mixed anxiety disorders, other specified anxiety disorders and anxiety disorder unspecified. The essential feature of panic disorder was described as recurrent attacks of severe anxiety (panic).

Generalised anxiety disorder was described as anxiety that was generalised and persistent. The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), within a section headed 'Anxiety Disorders', listed various manifestations of this disorder including generalised anxiety disorder, anxiety disorder due to a general medical condition, substance induced anxiety disorder and anxiety disorder not otherwise specified. Generalised anxiety disorder was characterised by at least six months of persistent and excessive anxiety and worry. The relevant section stated that panic attacks and agoraphobia occurred in the context of several of these aforementioned disorders. A panic attack was described as a discrete period in which there was a sudden onset of intense apprehension, fearfulness or terror often associated with feelings of impending doom. Anxiety was mentioned in relation

to agoraphobia. The Companion to Psychiatric Studies, sixth edition, discussed the relatively recent classification of panic disorders by DSM-III and ICD-10 and stated that 'The boundaries between panic disorder and generalised anxiety disorder, and panic disorder and agoraphobia are by no means clear'.

The Panel noted the difficulties in classifying and defining anxiety and panic attacks. The Panel noted that Cipramil was licensed to treat panic disorder, a condition characterised by discreet episodes of severe anxiety; it was not licensed to treat anxiety *per se*. The Panel considered that the claims at issue were not sufficiently clear about the licensed indication of the product; describing panic disorder as a severe form of anxiety implied that Cipramil was also specifically licensed to treat anxiety and that was not so. A breach of Clause 3.2 was ruled.

2 Claim 'Fewer reported adverse events than other SSRIs'

This claim, referenced to Edwards and Anderson (1999), appeared as a heading on page 5 above a table which favourably compared the total reports and total reactions of five classes of adverse reaction for Cipramil to those for fluvoxamine, fluoxetine, sertraline and paroxetine. The data for Cipramil appeared in a highlighted green column.

COMPLAINT

GlaxoSmithKline stated that it had complained to Lundbeck on a number of occasions in the past about the inappropriate use of these data in its promotional materials.

It was misleading to use spontaneous 'yellow card' reporting rate data, collected at different time points several years apart, to imply a lower incidence of adverse reactions to citalopram compared to other selective serotonin re-uptake inhibitors (SSRIs). Such reporting rates were open to numerous biases. This fact was acknowledged by both the MCA and the authors of the paper from which the table was taken. As the implied claim was not justified by the data presented nor supported by any comparative clinical trial data, it was misleading and thus in breach of Clause 7.2.

RESPONSE

Lundbeck referred to a previous case, Case AUTH/994/3/00, which concerned the use of the article by Edwards and Anderson to substantiate the claim 'Cipramil ... is associated with fewer adverse events than other SSRIs ... so patients are more likely to keep on taking it'. In that case the Panel had considered that '... the claim overstated the data from the review article to which it was referenced. The situation with regard to adverse events was more complicated than merely the number of adverse events'. This claim was ruled in breach of the Code. Lundbeck amended the claim to more accurately represent the data contained within the paper.

Lundbeck submitted that the claim and subsequent table did not imply a lower incidence of adverse

reactions to citalopram compared to other SSRIs. Lundbeck noted that the amended claim actually stated 'fewer reported adverse events than other SSRIs' and made no further claim or extrapolation of the data, and clearly carried specific details of the source of the data and time periods reportedly studied. These were in the first two years of the marketing of all the products, which was a comparable time period. Although the authors, and as stated by the complainant the MCA, acknowledged that spontaneous reports had advantages and disadvantages, a comparison of the post-marketing safety of four SSRIs was published by Price *et al* (1996). The authors were all members of the MCA or the Committee on Safety of Medicines (CSM). The authors concluded that it was possible to compare safety profiles of different products using spontaneous reports if one recognised any biases that were inherent. In the present instance however, no such claim had been made and the item only contained a representation of the facts as presented by Edwards and Anderson.

Lundbeck disagreed that this was a breach of Clause 7.2 of the Code.

As this item appeared to be the subject of protracted correspondence with SmithKline Beecham, Lundbeck stated that it had already given an undertaking to SmithKline Beecham that it would review and possibly amend the item in question. Despite not agreeing that the claim appeared to be in breach, as Lundbeck was in the process of amending its promotional materials, Lundbeck pointed out that it had given a written undertaking to SmithKline Beecham, on 8 December, that this item would be withdrawn, and undertook to not use the material in any inappropriate manner. The piece was withdrawn from circulation by 5 January.

PANEL RULING

The Panel noted that Case AUTH/994/3/00 concerned the claim 'Cipramil ... is associated with fewer adverse events than other SSRIs so patients are more likely to keep taking it' which appeared in a journal advertisement. It was alleged that the claim with regard to adverse events did not reflect the data, was inaccurate and could not be clinically substantiated. The claim was similarly referenced to Edwards and Anderson, a review article. The Panel had noted the discussion of the strengths and weaknesses of the various types of adverse event monitoring data in the paper. The Panel considered that the claim overstated the data from Edwards and Anderson. The situation with regard to adverse events was more complicated than merely the number of reported adverse events. The review article did not state that citalopram was associated with fewer adverse events than the other SSRIs. The Panel had ruled breaches of Clauses 7.2 and 7.7 of the Code.

Turning to the present case the Panel noted that the claim at issue was different to that in Case AUTH/994/3/00; the word 'reported' had been inserted and the claim appeared above a table which provided further data from Edwards and Anderson.

The Panel also noted Price *et al*, referred to by Lundbeck, which compared the post-marketing safety

of four SSRIs (fluoxetine, paroxetine, fluvoxamine and sertraline) including the investigations of symptoms occurring on withdrawal. The study authors noted that scrutiny of adverse drug reaction (ADR) reports led to the generation of signals of possible safety hazards, which might require further investigation using alternative data sources. The authors further stated that the interpretation of spontaneous ADR reports was subject to several biases and stated that if these were recognised and minimised it could be possible to compare safety profiles of different products.

The Panel noted the discussion of the strengths and weaknesses of such data in Edwards and Anderson as stated in Case AUTH/994/3/00. The Panel noted that Edwards and Anderson considered data from a meta-analysis of twenty short-term comparative studies, data from the CSM yellow card reports and data from the Prescription Event Monitoring System and the authors' conclusions about the advantages and disadvantages of each SSRI were based on these three sources, not yellow card reports alone. The authors noted that a disadvantage of citalopram was that 'It was comparatively new with therefore less chance of rare adverse reactions having been identified'.

The Panel considered that the claim at issue and the table of data invited the reader to directly compare the number of adverse event reports received for each SSRI listed and implied that it was fair to do so. That was not so. The comparison was unfair. A breach of Clause 7.2 of the Code was ruled.

3 Claim 'Cipramil is simple to initiate in panic disorder and does not require complex titration'

This claim appeared on page 8 beneath the heading of 'Simplicity in panic disorder' and above a table headed 'Cipramil v paroxetine' which compared various features of the two products.

COMPLAINT

GlaxoSmithKline stated that as the only other medication mentioned on page 8 was its product paroxetine, the implication of this claim was that paroxetine, compared to citalopram, was difficult to initiate in panic disorder and required a complex titration. Neither of these implications was correct. As this implied claim was misleading, it was in breach of Clause 7.2.

RESPONSE

Lundbeck stated that the above statement was clearly referenced to the Cipramil SPC and referred to Cipramil alone and did not in its interpretation suggested any comparison with paroxetine. The statement did not extrapolate the claim any further. Indeed, as could be noted from the Cipramil SPC, Cipramil, in panic disorder, was simply initiated with a 10mg tablet taken once a day for the first week increasing to 20mg once a day. Of note, clinical data available, for patients treated with Cipramil for panic disorder, suggested that the majority of patients were

managed on 20mg daily, though as noted in the SPC individuals might be titrated up to 60mg daily. The available dosage forms of Cipramil (10mg, 20mg and 40mg) allowed for this titration. Lundbeck considered that this treatment regimen was therefore simple to initiate and simple to titrate.

The table that appeared on the same page was clearly separately referenced and titled 'Cipramil vs paroxetine'. This table dealt with a number of issues such as selectivity, the effect on cytochromes (drug metabolism), protein binding etc that were clearly not connected to the claim at issue and did not suggest a link as indicated by the complainant. Lundbeck submitted that this clearly referenced claim was very specific and did not appear to be in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel did not accept that the claim was not linked to the table comparing various features of Cipramil and paroxetine therapy. The claim appeared immediately above the table; both the claim and the table referred to initiation of therapy. The Panel considered that the claim would be viewed as a comparison with paroxetine.

The Panel noted that in the treatment of panic disorder a single oral dose of Cipramil 10mg was recommended for the first week before increasing the dose to 20mg daily. The dose might be further increased, up to a maximum of 60mg daily dependent on individual patient response. An optimal dose of 20-30mg daily was indicated in a clinical study (ref SPC).

With regard to paroxetine the Panel noted that the Seroxat SPC stated that in panic disorder the recommended dose was 40mg daily. Patients should be started on 10mg per day and the dose increased weekly in 10mg increments according to the patient's response.

The Panel considered that in the context of the page on which it appeared the claim gave the misleading impression that paroxetine therapy was more difficult to initiate and required a more complex dose titration regimen than Cipramil therapy. This was not so. A breach of Clause 7.2 was ruled.

4 Claim 'Can be taken any time of the day'

This claim appeared on page 8 in the table comparing various features of Cipramil and paroxetine therapy. A tick appeared in the Cipramil column and a cross in the paroxetine column.

COMPLAINT

GlaxoSmithKline stated that it was incorrect to place a cross against paroxetine and a tick for Cipramil in this comparative table. The SPC for paroxetine simply stated that it was recommended to be given in the morning. This did not mean it could not be taken at any other time of day, which was the interpretation readers of this item could reach. Indeed, GlaxoSmithKline was aware that some patients were advised by their doctor to take paroxetine in the

evening. It was alleged that the table was misleading in breach of Clause 7.2.

RESPONSE

Lundbeck stated that the paroxetine SPC recommended that paroxetine be administered once daily in the morning with food. This recommendation was clearly stated in a sub-section of the drug posology for paroxetine. The comparison, between product SPCs, was valid. It might be the case that some doctors may suggest any treatment regimen, even one that did not follow the licensed recommendation. It would be highly inappropriate for Lundbeck, to compare usage outside of the licensed recommendations. Lundbeck did not consider that this comparison was misleading in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that the Seroxat SPC stated that 'It is recommended that 'Seroxat' be administered once daily in the morning with food'. The Panel noted that this was a recommendation only, the SPC did not state that Seroxat must be taken in the morning and so, in the Panel's view, the administration of paroxetine at a different time of the day was not prohibited. The Panel considered that the cross in the paroxetine column, against the claim 'Can be taken at any time of the day' was not a fair reflection of the data in the Seroxat SPC. A breach of Clause 7.2 was ruled.

5 Claim '40mg OD – for severe and recurrent depression'

This claim appeared on page 9 below the heading 'Easy to prescribe'.

COMPLAINT

GlaxoSmithKline stated this dosage for this indication was not mentioned in the citalopram SPC. After initiation of 20mg/day in depressed patients, the SPC stated that the dose might be increased to a maximum of 60mg/day, depending on response. Thus, to state in this way that 40mg/day was 'the' dose for severe and recurrent depression, ignoring the possibility of the need for 60mg/day as specified in the marketing authorization, was misleading and therefore in breach of both Clause 3.2 and 7.2.

Lundbeck had already conceded, in previous correspondence relating to complaints against other Cipramil promotional material, that '40mg OD-for severe recurrent depression' was an inaccurate statement and had committed to withdraw from use separate promotional items that contained this claim.

RESPONSE

Lundbeck stated that it was never its intention to suggest an indication for the 40mg dosage, merely to reflect findings that suggested that more severe cases of depression could respond to higher doses of Cipramil (Montgomery *et al* 1994). Lundbeck accepted that the statement could be interpreted inaccurately; it had already advised SmithKline

Beecham that this statement would be removed immediately, and in fact it did not appear on current materials.

PANEL RULING

The Panel noted that the Cipramil SPC stated that when treating depression Cipramil should be administered as a single oral dose of 20mg daily. Dependent on individual patient response this might be increased to a maximum of 60mg daily. The Panel noted that a specific dosage for severe and recurrent depression was not mentioned in the SPC. The Panel considered the claim at issue was not a fair reflection of the data in the Cipramil SPC and was misleading as alleged. Breaches of Clauses 3.2 and 7.2 were ruled.

6 Prescribing Information

COMPLAINT

GlaxoSmithKline stated that the 'Adverse Event' section of the prescribing information given on the detail aid mentioned the following adverse events: nausea, tremor, somnolence, dry mouth and 'withdrawal symptoms' (sic). This totalled five different adverse events, if the unspecified 'withdrawal symptoms' were counted as a single event.

In contrast, the Cipramil SPC listed the following under 'Undesirable effects': nausea (three times), somnolence (twice), dry mouth (twice), increased sweating (twice), tremor (twice), dizziness (twice), paraesthesia (twice), headache (twice), anxiety (twice), abnormal accommodation, insomnia, agitation, nervousness, constipation, diarrhoea, palpitation, asthenia, rash, pruritis, migraine, abnormal vision, taste perversion, sleep disorder, decreased libido, impaired concentration, abnormal dreaming, amnesia, increased appetite, anorexia, apathy, impotence, suicide attempt, confusion, yawning, dyspepsia, vomiting, abdominal pain, flatulence, increased salivation, weight decrease, weight increase, postural hypertension, tachycardia, rhinitis, micturition disorder, polyuria, ejaculation failure, female anorgasmia, fatigue, myalgia, extrapyramidal disorder, convulsions, tinnitus, euphoria, increased libido, coughing and malaise. This totalled fifty-seven different adverse events.

Clearly the prescribing information on this detail aid failed to adequately give '... in an abbreviated form, the substance of the relevant information in the summary of product characteristics'. Thus, it was in breach of Clause 4.2.

RESPONSE

Lundbeck stated that GlaxoSmithKline had only listed four adverse events and not the five that were actually listed in the Cipramil SPC as 'not seen at an equal incidence among placebo treated patients'. (ie nausea, sweating, tremors, somnolence and dry mouth). There was also a general statement about withdrawal.

In data presented to the regulatory authorities (in this instance the MCA) from all clinical trials the most likely adverse events to have a causal association were those that were reported at rates significantly higher than placebo (from the appropriate studies). Consequently these were reflected in the Cipramil prescribing information.

The relevance of adverse events occurring at a comparable or lower rate than placebo was debatable unless obviously of a serious nature. Due to the regulatory formatting requirement of the SPC at the time of the licensing of Cipramil there was a comprehensive list of adverse events, occurring in the Cipramil clinical trials programme, whether they were significantly different to placebo or not.

Lundbeck submitted that the Cipramil prescribing information included, as required by Clause 4.2 of the Code, - 'a succinct statement of the side effects'. Lundbeck did not consider therefore that the prescribing information was in breach of Clause 4.2 of the Code.

Lundbeck stated that it had already agreed in correspondence with SmithKline Beecham that the detail aid noted above was in the process of revision and withdrawal.

PANEL RULING

The Panel noted that Clause 4.2 set out the content of prescribing information and required, *inter alia*, 'a succinct statement of the side-effects, precautions and contra-indications relevant to the indications in the advertisement, giving, in an abbreviated form, the substance of the relevant information in the summary of product characteristics or data sheet'. Clause 4.1 of the Code stated that the information listed in Clause 4.2 must be provided. Failure to do so would therefore be a breach of Clause 4.1.

The Panel noted that the 'Undesirable effects' section of the SPC and the 'Adverse Events' section of the prescribing information listed those adverse events which were most commonly associated with Cipramil and which had occurred with a greater incidence than in placebo-treated patients. Both documents also referred to withdrawal reactions which had been reported in association with SSRIs including Cipramil.

The Panel noted that following the information given above, the SPC then listed treatment emergent adverse events reported in clinical trials (n=2985). Fifteen events were listed as frequent ($\geq 5-20\%$), thirty-four as less frequent ($1- < 5\%$) and eight as rare ($< 1\%$). None of this information was included in the prescribing information. The Panel considered that by not referring at all to treatment emergent events the prescribing information, with regard to side effects, did not provide the substance of the relevant information in the SPC. A breach of Clause 4.1 was ruled.

Complaint received 17 January 2001

Case completed 22 February 2001

CONSULTANT SURGEON v MERCK SHARP & DOHME

Fosamax 'Dear Doctor' letter

A consultant surgeon complained that the prescribing information was illegible on a letter about Fosamax sent by Merck Sharp & Dohme.

The Panel noted that the letter had been printed on off-white paper and the prescribing information was printed in pale grey. The size of the prescribing information met the recommendation in the supplementary information to the Code in that a lower case letter 'x' was not less than 1mm in height. The Panel did not, however, consider that the contrast between the colour of the text and the background was adequate. The prescribing information was difficult to read. It had not been given clearly and legibly. A breach of the Code was ruled.

A consultant surgeon complained about a Fosamax 70mg (alendronate) 'Dear Doctor' letter (ref 11-01 FSM.00.GB.60630.L.2c.CW.1000) issued by Merck Sharp & Dohme Limited.

COMPLAINT

The complainant stated that he had written to Merck Sharp & Dohme complaining that the prescribing information on promotional literature for Fosamax 70mg was illegible. The complainant no longer possessed a copy of the material in question but clearly his view that the prescribing information was quasi-illegible was shared by others. The complainant provided a copy of a letter about the matter which had been sent to him by a colleague.

RESPONSE

Merck Sharp & Dohme stated that it had already been in touch with the complainant following his comment upon the legibility of the prescribing information on the letter. The relevant correspondence was provided.

Merck Sharp & Dohme submitted that the prescribing information on the back of the letter conformed fully with the requirements of Clause 4.1 and the supplementary information. The font was Times Roman, 10 point bold for the main heading, and 7/8 for the rest of the text. A lower case 'x' was

1.1 mm in height. The headings were emboldened with each section starting on a new line, and each line was less than 100 characters in length. Whilst the print was grey, Merck Sharp & Dohme believed the contrast was adequate for good legibility in any reasonable lighting conditions. Also, in this particular case, a copy of the summary of product characteristics, in a larger type typeface and black and white, was enclosed with the mailing. Merck Sharp & Dohme stated that it took the complainant's comments seriously, and would in future use black for prescribing information as was the company's usual practice.

PANEL RULING

The Panel examined the letter in question. It had been printed on off-white paper and the prescribing information was printed in pale grey. The prescribing information had been printed in two columns. Clause 4.1 of the Code stated that prescribing information must be provided in a clear and legible manner. The supplementary information to Clause 4.1, Legibility of Prescribing Information, made recommendations about, *inter alia*, type size and contrast which would help achieve clarity. The Panel noted that the size of the prescribing information met the recommendation in the supplementary information in that a lower case letter 'x' was not less than 1mm in height. The Panel did not, however, consider that the contrast between the colour of the text and the background was adequate. The prescribing information was difficult to read. It had not been given clearly and legibly. The Panel therefore ruled a breach of Clause 4.1 of the Code.

Complaint received 11 January 2001

Case completed 15 February 2001

SANOFI-SYNTHÉLABO v YAMANOUCHI PHARMA and GLAXOSMITHKLINE

Flomax MR journal advertisement

Sanofi-Synthélabo complained about a journal advertisement for Flomax MR (tamsulosin) issued by Yamanouchi Pharma and Glaxo Wellcome. The foreground of the advertisement featured a photograph of a man, representing a farmer, with his hand on a standpipe superimposed on a scene of open countryside. Cartoon farmyard animals were enjoying being sprayed with water from the standpipe. In the middle ground a cartoon woman was smiling and leaning over a gate with a mug in her hand. The headline read 'Relief all round'. Immediately beneath the headline were three stabpoints: 'Rapid and sustained relief of symptoms', 'Minimal effect on blood pressure' and 'Delays the need for surgery'. Sanofi-Synthélabo alleged that there was insufficient justification for the headline claim, which appeared to be exaggerated and all-embracing.

The Panel noted that Sanofi-Synthélabo had given no reasons at all as to why it considered that the headline 'Relief all round' was exaggerated and all-embracing. Yamanouchi had stated that the intention of the advertisement and the headline was to draw attention to two factors in relation to the treatment of benign prostatic hyperplasia (BPH); firstly, the benefits to the patient in terms of symptom relief and improved urinary flow and secondly, that the benefits would extend beyond the patient himself, particularly to partners and close family.

The Panel noted that Abrams *et al* demonstrated that in BPH Flomax therapy significantly improved urinary flow rate, irritative and obstructive symptom scores and symptoms of nocturia and hesitancy. Compared to placebo, maximum urinary flow was significantly improved and there was a greater decrease in total symptom score. Significantly more Flomax-treated patients than placebo-treated patients had a greater than 25% decrease in total symptom score at 12 weeks. Thus, in terms of the patient the Panel considered that the headline was not exaggerated or all-embracing.

The Panel noted that Sells *et al*, using a quality of life questionnaire, confirmed the presence of significant morbidity in the partners of men with BPH. The degree of partner morbidity was related to the severity of the patient's symptoms. There was no specific claim regarding the effect of the treatment of BPH on the patient's partner. The matter had been raised by Yamanouchi and not by the complainant. The inclusion of a cartoon woman smiling in the advertisement might be seen as implying that she too was pleased with the improvement in her husband's condition. In the Panel's view this would be a natural reaction and was not unreasonable. In the circumstances the Panel did not accept that the advertisement was exaggerated or all-embracing with regard to effects on the partner. No breach of the Code was ruled.

Sanofi-Synthélabo complained about a journal advertisement (ref Yam 62474N/WBR/Aug 2000) for Flomax MR (tamsulosin) issued by Yamanouchi Pharma Ltd and Glaxo Wellcome. The foreground of

the advertisement featured a photograph of a man, representing a farmer, with his hand on a standpipe superimposed onto a scene of open countryside; cartoon farmyard animals were enjoying being sprayed with water from the standpipe. In the middle ground a cartoon woman was smiling and leaning over a gate with a mug in her hand. The headline read 'Relief all round'. Immediately beneath the headline were three stabpoints: 'Rapid and sustained relief of symptoms'; 'Minimal effect on blood pressure'; 'Delays the need for surgery'.

COMPLAINT

Sanofi-Synthélabo alleged that the headline was in breach of Clause 7.8 of the Code; from correspondence with Yamanouchi the company did not consider that there was sufficient justification for the claim, which appeared to be exaggerated and all-embracing.

RESPONSE

Yamanouchi Pharma responded on behalf of itself and GlaxoSmithKline.

Yamanouchi provided copies of earlier correspondence to show that it did not understand the basis on which Sanofi-Synthélabo considered the headline to be all-embracing. In its response to Sanofi-Synthélabo, Yamanouchi had explained the intentions behind the use of the headline and justified its use. In view of the unclear complaint, Yamanouchi had asked Sanofi-Synthélabo to let it know if its interpretation of the complaint was incorrect. However, Sanofi-Synthélabo chose not to give Yamanouchi any further indication as to why the advertisement could be considered all-embracing, but instead chose to refer it to the Authority. Unfortunately, the letter of complaint still gave no further explanation as to why the headline could be considered all-embracing, and Sanofi-Synthélabo had now extended its complaint and considered that the advertisement was exaggerated and all-embracing.

Yamanouchi explained that Flomax MR was licensed for the treatment of the functional symptoms of benign prostatic hyperplasia (BPH). BPH was a benign enlargement of the prostate gland, which occurred as a consequence of ageing. This led to narrowing of the urethra, which caused the symptom complex associated with BPH. Patients suffering from BPH might present with a variety of symptoms, which could be divided into irritative and obstructive symptoms (Abrams *et al* 1995). The irritative symptom cluster was derived from the combined aggregate of urgency, nocturia, daytime frequency,

and dysuria (burning sensation). The obstructive symptom cluster was derived from the combined aggregate of hesitancy, intermittency, impairment of size and force of urinary stream (poor flow), terminal dribbling and sensation of incomplete voiding (emptying of the bladder). These same symptoms formed the Boyarsky Symptom Score (Boyarsky *et al* 1995), which was the symptom score used in the pivotal registration studies for Flomax MR.

Yamanouchi stated that the intention of its advertisement and the headline was to draw attention to two factors in relation to the treatment of BPH, firstly the effect of Flomax MR across the irritative and obstructive clusters and urinary flow rate (Q_{max}), and secondly, that the benefits would extend beyond the patient himself, particularly to partners and close family.

The headline 'Relief all round' was originally tested with GPs at concept stage on a similar advertisement in order to ensure that the intended messages were, in fact, the ones being perceived. The transcripts showed that whilst the alternative execution of the advertisement was not well received, the messages were received as intended, ie a relief of symptoms with an improved flow, and relief for partners/close family. This was illustrated, for example, where there was agreement that the message related to 'symptom relief ... yes, yes, which is great because that's what the majority of patients are coming for'; and the response to the question 'But what does relief all round mean?' was 'Everyone's happy, the GP is happy, patient's happy, patient's wife is happy, the patient's family is happy ...'.

Yamanouchi addressed each interpretation of the advertisement.

'Relief all around' relating to symptoms and urinary flow rate (Q_{max})

Yamanouchi explained that the severity or 'bothersomeness' of symptoms that together comprised the aggregate scores related to obstructive and irritative clusters would vary between patients.

One of the pivotal registration studies that formed the Flomax MR product licence approval was a 12 week double-blind, randomised, placebo controlled study, investigating the efficacy and safety of tamsulosin amongst patients with symptomatic BPH (Abrams *et al*). The primary measures of efficacy were Q_{max}, determined by the free flow measurements and the total Boyarsky Symptom Score.

The study showed that tamsulosin significantly improved maximum urinary flow rate (Q_{max}) in the intention to treat (ITT) population (n=187), as measured by free-flow measurements (mls/second), compared with the placebo group (n=94) from baseline to study end. The mean increase in Q_{max} from baseline to endpoint was 0.4ml/s (3.8%) in the placebo treated group and 1.4ml/s (13.1%) in the tamsulosin treated group (p=0.028).

In terms of the total Boyarsky Symptom Score, there was a significant improvement in the ITT analysis from baseline to study end. At endpoint the mean decrease in total symptom score from baseline was 2.2 points (23.7%) in the placebo treated group and 3.4

points (35.8%) in the tamsulosin treated group (p=0.002).

The results of the study also demonstrated that there was a significant improvement in both of the irritative and obstructive symptom clusters for the tamsulosin ITT efficacy population compared to placebo from baseline to study end (p=0.013 and 0.014 respectively).

Yamanouchi stated that Flomax MR had been demonstrated to significantly improve flow rate, total Boyarsky Symptom Score, and the two individual symptom clusters, ie obstructive and irritative, and therefore the company considered that this justified the claim 'relief all round', and thus it was not in breach of Clause 7.8 of the Code.

'Relief all round' relating particularly to partners and close family

Yamanouchi stated that it was inevitable that symptoms which impacted on patients' lives would also impact on their partners and close family.

Yamanouchi stated that in a website survey of men with lower urinary tract symptoms, which included 467 respondents in the UK, it was found that 41% planned their day around the availability of a toilet; 31% avoided travelling long distances because of the need to urinate frequently and 20% avoided going to the cinema/opera/theatre because of the need to urinate frequently. These restrictions would inevitably impact upon partners and close family members.

This impact had been investigated and published (Sells *et al* 2000). The study investigated morbidity in partners as a consequence of the patients' benign prostatic condition. The results showed that: 42% said they were tired because of being woken at night; 47% said that their social life was affected by their husband's symptoms; 27% said their husband's symptoms made it difficult to do essential tasks; 66% said they were upset by the distress that their husbands suffered because of their symptoms.

Yamanouchi noted that a Xatral advertisement issued by Lorex Synthélabo (now Sanofi-Synthélabo), which highlighted the effects of BPH on partners and close family, was being used by consultants at meetings to make this very point to the audience. For example, the picture was shown at the Royal Society of Medicine meeting, Key Advances in Benign Prostatic Disease, held on 30 November 2000. The main text stated '... not only for the male patient, but also for those around him.' [emphasis added]

Yamanouchi stated that Flomax MR was licensed to treat symptoms. As a result, the company maintained that when a patient's symptoms improved their partner's distress/anxiety was also alleviated, ie they too felt relief, 'Relief all round'.

Yamanouchi stated the meaning of the two components of the headline as defined in the New Shorter Oxford English Dictionary:

Relief – 'the alleviation of or deliverance from pain, distress, anxiety, monotony etc; the feeling accompanying this, mental relaxation'. Yamanouchi stated that Flomax MR provided alleviation of the symptoms of BPH, and, therefore, the associated

distress and anxiety which accompanied the very real concerns patients had about wetting themselves and from their disturbed nights. Yamanouchi noted the definition of alleviation: 'the action of lightening weight, gravity, severity or pain, relief, mitigation'. The relevant context here was that Flomax MR would lighten the severity (of the functional symptoms of BPH). The word 'relief' was commonly used in publications in the context of 'symptom/symptomatic relief', ie the authors showed a reduction in symptoms or symptom score and not total abolition of symptoms.

All round – 'everywhere around; in all respects; for all concerned'. Yamanouchi noted that the first of these definitions was obviously not relevant as it was geographical. In terms of the second, 'in all respects', the company submitted that to claim that in the context of BPH, Flomax MR provided relief in all respects was not exaggerated as the licensed indication was the treatment of functional symptoms of BPH and, as mentioned previously, it relieved the irritative and obstructive symptom clusters and urinary flow rate (Qmax). In terms of the third definition 'for all concerned', in the context of the advertisement, it would seem obvious that the 'all concerned' related to the patient, his wife and close family (a view supported in practice from the concept testing). Yamanouchi stated that as discussed above, it was widely acknowledged that partners and families were affected by the patient's symptoms, and therefore, when these improved the feeling accompanying this distress/anxiety was alleviated, ie they felt relief.

In conclusion Yamanouchi stated that it did not consider that the headline in the context of this advertisement, for either of the interpretations, was exaggerated, or all-embracing and it was not in breach of Clause 7.8 of the Code.

PANEL RULING

The Panel noted that Sanofi-Synthelabo gave no reasons at all as to why it considered that the headline 'Relief all round' was exaggerated and all-embracing.

Yamanouchi stated that the intention of the advertisement and the headline was to draw attention to two factors in relation to the treatment of BPH, firstly the benefits to the patient in terms of symptom relief and improved urinary flow and secondly, that the benefits would extend beyond the patient himself, particularly to partners and close family.

The Panel noted that Abrams *et al* demonstrated that in BPH Flomax therapy significantly improved urinary flow rate (p=0.04), irritative (p=0.013) and obstructive (p=0.014) symptom scores and symptoms of nocturia (p=0.022) and hesitancy (p=0.004). Compared to placebo, maximum urinary flow was significantly improved (p=0.028) and there was a greater decrease in total symptom score (p=0.002). Significantly more Flomax-treated patients than placebo-treated patients had a greater than 25% decrease in total symptom score at 12 weeks (p<0.001). Thus, in terms of the patient the Panel considered that the headline was not exaggerated or all-embracing.

The Panel noted that Sells *et al*, using a quality of life questionnaire, confirmed the presence of significant morbidity in the partners of men with BPH. The degree of partner morbidity was related to the severity of the patient's symptoms. The Panel noted that there was no specific claim regarding the effect of the treatment of BPH on the patient's partner. The matter had been raised by Yamanouchi and not by the complainant. The inclusion of a cartoon woman smiling in the advertisement might be seen as implying that she too was pleased with the improvement in her husband's condition. In the Panel's view this would be a natural reaction and was not unreasonable. In the circumstances the Panel did not accept that the advertisement was exaggerated or all-embracing with regard to effects on the partner.

The Panel ruled no breach of Clause 7.8 of the Code.

Complaint received **16 January 2001**

Case completed **27 February 2001**

BIOGLAN LABORATORIES v YAMANOUCHI PHARMA

Zineryt journal advertisement

Bioglan Laboratories complained about an advertisement for Zineryt (erythromycin/zinc acetate complex) issued by Yamanouchi Pharma. The advertisement read 'Zinc makes a difference. Adding to the effectiveness of the highest strength of topical erythromycin available on prescription. Zinc is active against both antibiotic-resistant propionibacteria and fully-sensitive strains. Zinc also reduces sebum excretion and aids wound healing'.

Bioglan noted that the claim that zinc added to the effectiveness of topical erythromycin was supported by three references which related to zinc's potential as an agent to suppress sebum and against resistant organisms in acne; activities which were not mentioned in the Zineryt summary of product characteristics (SPC). Bioglan stated that the data in these studies had not been validated clinically and the authors warned against extrapolation to the clinical setting. By supporting the claim for zinc's added effectiveness exclusively with these studies, Yamanouchi was implying a clinical activity which was unproven and not supported by the SPC. Bioglan alleged that this was misleading.

The Panel considered that the claim that 'Zinc makes a difference' was not unreasonable given that the SPC stated that topical zinc was an established aid to wound healing.

The Panel noted that claims in promotional material were assumed to relate to the clinical situation unless otherwise stated. The Code did not prohibit the use of data derived from *in vitro* studies or studies in healthy volunteers *per se* but care must be taken with the use of such data so as not to mislead as to its significance. The Panel noted that the advertisement referred to the activity of zinc against antibiotic-resistant propionibacteria and fully-sensitive strains and that it reduced sebum excretion. There was no mention of these features in the SPC. The available data was *in vitro* data and a volunteer study. The Panel noted the authors' comments regarding the relevance of the results. The claims implied specific clinical activity which had not been demonstrated. The claims were misleading and a breach of the Code was ruled.

Bioglan noted that the supporting reference to the claim 'Zinc is active against both antibiotic-resistant propionibacteria and fully sensitive strains', Farmery *et al*, contained *in vitro* data only and alleged that the failure to qualify this claim as *in vitro* activity was an important omission as it left the *in vitro/in vivo* context open to interpretation by the reader. It was reasonable to presume that some readers might expect this claim to have been validated clinically *in vivo*, a significant misconception. Bioglan alleged that the claim was ambiguous and misleading.

The Panel accepted that doctors would be aware that antibiotic sensitivity tests were performed *in vitro* but noted that in this case Farmery *et al* had stated that it was yet to be determined whether their results would be seen during *in vivo* use. The Panel considered that in the circumstances readers should have been made aware that similar data had yet to be generated *in vivo*. The Panel considered that the claim was misleading as alleged. A breach of the Code was ruled.

Bioglan Laboratories Limited complained about an advertisement (ref Yam 62559D/WBR/Aug 2000) for Zineryt (erythromycin/zinc acetate complex) issued by Yamanouchi Pharma Ltd.

The advertisement read 'Zinc makes a difference. Adding to the effectiveness of the highest strength of topical erythromycin available on prescription. Zinc is active against both antibiotic-resistant propionibacteria and fully-sensitive strains. Zinc also reduces sebum excretion and aids wound healing'.

In its response Yamanouchi provided some background information and explained that Zineryt was licensed for the topical treatment of acne vulgaris in the UK. It consisted of erythromycin 4% and zinc acetate 1.2% in an ethanol vehicle. Patients should apply Zineryt to the whole area affected by acne twice daily for a period of 10 to 12 weeks.

Yamanouchi stated that multiple factors were involved in the pathogenesis of acne. The three most significant were:

Androgenic hormones Under androgen stimulation, sebaceous glands enlarged and increased their sebum production. Before puberty, the responsible androgens were secreted by the adrenal gland. During puberty, the addition of gonadal androgens provided further sebaceous gland stimulation.

Follicular obstruction For acne to occur, outlet obstruction of the follicular canal was required. This obstruction occurred because of accumulation of adherent keratinized cells within the canal, to form an impaction. The cause of follicular obstruction was not known, but it might also be influenced by androgens.

Bacteria Proximal to the follicular outlet obstruction, sebum and keratinous debris accumulated. This provided an attractive environment for the growth of anaerobic bacteria, specifically *Propionibacterium acnes*. These bacteria produced lipase enzymes that hydrolyzed the sebaceous lipids, resulting in the release of free fatty acids, which were presumed to cause inflammation. *P. acnes* played other roles in the pathogenesis of acne; for example, these bacteria were chemotactic for neutrophils.

1 Claim that zinc adds to the effectiveness of topical erythromycin

COMPLAINT

Bioglan Laboratories noted that this claim was supported by three references which related to zinc's potential as an agent to suppress sebum and against resistant organisms in acne; activities which were not mentioned in the Zineryt summary of product characteristics (SPC). Bioglan stated that the data in these studies had not been validated clinically and the

authors warned against extrapolation to the clinical setting. By supporting the claim for zinc's added effectiveness exclusively with these studies, Yamanouchi was implying a clinical activity which was unproven and not supported by the SPC. Bioglan alleged that this was misleading in breach of Clause 7.2 of the Code.

RESPONSE

Yamanouchi stated that Zineryt was a licensed combination product containing two active ingredients, erythromycin and zinc acetate. The Medicines Control Agency (MCA) did not grant licences to combination products unless each active ingredient had been shown to contribute to the effectiveness of the product.

Yamanouchi noted that the Code required that any claim made in an advertisement be capable of substantiation and that it must not mislead directly or by implication. It was not a requirement for all relevant references to be cited. In this instance, the claim could be substantiated solely from the terms of the product licence, as explained above. Therefore, the claim could not be misleading as the added effectiveness of zinc had been demonstrated to the satisfaction of the MCA, resulting in the granting of the licence.

Yamanouchi stated that contrary to the statement made in the complaint, it was not supporting the claim of the added effectiveness of zinc exclusively using the referenced studies. The three published references cited had been chosen as complementary information on the effectiveness of zinc, which was acknowledged by the terms of the product licence.

Yamanouchi summarised the three publications referenced in the advertisement:

Holland *et al* (1992) assessed the effect of zinc acetate on erythromycin-resistant and erythromycin-sensitive strains of *P. acnes*, obtained from acne patients and grown together *in vitro*. When added to the highest concentration of erythromycin, zinc acetate inhibited the growth of erythromycin-resistant bacteria even though the same concentration of erythromycin alone did not.

It was reported in this paper that the results supported the hypothesis that erythromycin alone would not inhibit erythromycin-resistant *P. acnes*. The authors also stated it to be possible that treatment with a zinc-erythromycin mixture would reduce therapeutic failure because the frequency of erythromycin-resistant *P. acnes* colonising the skin would be reduced. In addition, the authors mentioned that the efficacy of the erythromycin/zinc preparation might not reside solely in its antimicrobial effect, but on another mode of action, such as affecting the inflammatory response.

Farmery *et al* (1994) was an *in vitro* study which assessed the minimum inhibitory concentration (MIC) of zinc acetate, as well as azelaic acid and benzoyl peroxide, against antibiotic-resistant (to erythromycin, tetracycline or both) and antibiotic-sensitive propionibacteria isolated from the skin of acne patients. The MIC of zinc acetate was the same for

both antibiotic-sensitive and antibiotic-resistant strains. For fully antibiotic-sensitive strains, zinc acetate was less active than either antibiotic. However, against erythromycin-resistant strains, zinc acetate was more effective than erythromycin.

The authors' recommendation was that these agents (ie zinc acetate, azelaic acid and benzoyl peroxide) were prescribed either concomitantly with, or immediately following, courses of oral or topical antibiotics for acne in order to minimise the selection and dissemination of antibiotic-resistant strains of *P. acnes*.

Piérard-Franchimont *et al* (1995) was a double-blind randomised study in which fourteen healthy volunteers applied Zineryt to one half of their forehead and 4% erythromycin to the other half twice daily for 12 weeks. At the start of the trial and after weeks 3, 6, 9 and 12 the casual sebum level, sebum excretion rate and total area covered with lipid spots were assessed.

The results showed that the casual sebum level was reduced on both sides of the forehead, significantly more on the Zineryt-treated side after 6 weeks' treatment and until the end of the trial. A significant reduction was found in sebum excretion rate at the Zineryt-treated site at 3, 6 and 9 weeks compared with the erythromycin-treated site. The zinc-supplemented formulation demonstrated a significant reduction of total area of lipid spots at 1 hour and 4 hours post application at weeks 3, 6, 9 and 12 compared with 4% erythromycin. This further supported the finding that Zineryt decreased sebum excretion rate. The results of this study confirmed that after 12 weeks' use of Zineryt sebum secretion was significantly reduced by over 20% compared with erythromycin alone.

Yamanouchi noted that when using healthy volunteer data to support claims, guidance in the supplementary information to Clause 7.2 advised that data must not mislead and should only be extrapolated to the clinical situation when it could be shown to be of direct relevance and significance. The company contended that this study was not being used in isolation to support the claim as the claim itself was in accordance with the product licence and therefore, it could be substantiated. The use of this as a supporting reference therefore could not mislead the reader into believing that Zineryt had any properties that were not of direct relevance and significance to the treatment of acne.

Yamanouchi stated that as could be seen from the above summaries all three references were consistent with the terms of the product licence. As such, therefore, they could not be misleading and consequently, there was no breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that the advertisement included the claim that 'Zinc makes a difference'. This was referenced to Piérard-Franchimont *et al*, Holland *et al* and Farmery *et al*. The advertisement stated that zinc added to the effectiveness of the highest strength of topical erythromycin. It was active against both

antibiotic-resistant propionibacteria and fully-sensitive strains (Farmery *et al*). It also reduced sebum excretion (Piérard-Franchimont *et al*) and aided wound heading (SPC). The Panel considered that the claim that 'Zinc makes a difference' was not unreasonable given that Section 5.1 of the Zineryt SPC headed 'Pharmacodynamic properties' stated that topical zinc was an established aid to wound healing. There was no reference in the SPC to its efficacy versus antibiotic-resistant/fully sensitive strains of propionibacteria or to its ability to reduce sebum excretion.

The Panel noted that Holland *et al* was a study designed to determine whether, in an *in vitro* model, the presence of zinc with erythromycin would inhibit the growth of erythromycin-resistant and erythromycin-sensitive *P. acnes*. The results demonstrated a positive effect for zinc and suggested that the presence of zinc with erythromycin would help to prevent the selection of erythromycin-resistant bacteria. The authors stated that it was possible that treatment with a zinc/erythromycin mixture would reduce therapeutic failure because the frequency of erythromycin-resistant *P. acnes* colonizing the skin would be reduced. The authors concluded, however, by stating that the results obtained might not extrapolate to the *in vivo* situation because not all erythromycin-resistant cells of *P. acnes* might behave in the same manner; there were at least four phenotypes of erythromycin-resistant *P. acnes* cells. The authors also noted that the efficacy of the erythromycin/zinc preparation might not reside solely in its antimicrobial effect but on another mode of action, such as affecting the inflammatory response.

The Panel noted that the introduction to Farmery *et al* referred to three broad spectrum antibacterial agents being currently available for topical treatment of acne. These were azelaic acid, benzoyl peroxide and zinc acetate. Zinc acetate was only available in combination with erythromycin. Theoretically the compounds should be equally as active against antibiotic-resistant propionibacteria as against fully sensitive strains. Furthermore, because they inhibited bacterial growth by interfering with more than one physiological function, resistance to them was far less likely to emerge than to antibiotics. The Panel noted that Farmery *et al* showed that, in standard laboratory conditions, there was no difference between antibiotic-sensitive and antibiotic-resistant propionibacteria in their degree of susceptibility to three antibacterial agents including zinc acetate. The authors, however, noted that the *in vivo* antipropionibacterial activity would depend on the original concentration in the formulation, the ultimate concentration in the pilo-sebaceous follicle and the stability of the product in the skin environment. Therefore the *in vitro* activity might not reflect *in vivo* efficacy; there was no evidence of the antipropionibacterial activity of zinc acetate when applied to human skin. The paper ended by stating that similar studies were now required to ascertain whether the predicted similar effect against antibiotic-resistant propionibacteria occurred during *in vivo* use.

Piérard-Franchimont *et al* compared the ability of Zineryt and erythromycin lotions to suppress sebum

production in fourteen male volunteers with seborrhoea on the forehead. The study showed that, compared to the erythromycin lotion, and to baseline, sebum output was significantly reduced after 12 weeks' use of Zineryt. The authors postulated that this could theoretically be beneficial in the treatment of acne and might, in part, explain the better clinical effect of Zineryt over erythromycin lotion.

The Panel noted that all claims in promotional material were assumed to relate to the clinical situation unless otherwise stated. The Code did not prohibit the use of data derived from *in vitro* studies or studies in healthy volunteers *per se* but the relevant supplementary information to Clause 7.2 stated that care must be taken with the use of such data so as not to mislead as to its significance. The extrapolation of such data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance. The Panel noted Yamanouchi's submission that for a combination product to be licensed each active ingredient had to be shown to contribute to the effectiveness of the product. The pharmacodynamic properties were described in the SPC. Erythromycin was known to be efficacious at 4% in the topical treatment of acne vulgaris. Zinc topically was established as an aid to wound healing. The zinc acetate was solubilised by complexing with the erythromycin and delivery of the complex was enhanced by the chosen vehicle.

The Panel noted that the advertisement referred to the activity of zinc against antibiotic-resistant propionibacteria and fully sensitive strains and that it reduced sebum excretion. There was no mention of these features in the SPC. The available data was *in vitro* data and a volunteer study. The Panel noted the authors' comments regarding the relevance of the results. The claims implied specific clinical activity which had not been demonstrated. The claims were misleading and a breach of Clause 7.2 of the Code was ruled.

2 Claim that zinc is active against both antibiotic-resistant propionibacteria and fully sensitive strains

COMPLAINT

Bioglan noted that the supporting reference contained *in vitro* data only. The failure to qualify this claim as *in vitro* activity was an important omission as it left the *in vitro/in vivo* context open to interpretation by the reader. It was reasonable to presume that some readers might expect this claim to have been validated clinically *in vivo*, a significant misconception. Bioglan alleged that the statement was both ambiguous and misleading in breach of Clause 7.2 of the Code.

RESPONSE

Yamanouchi stated that it did not consider that this claim was either ambiguous or misleading because it was supported by Farmery *et al*.

Farmery *et al* clearly and unambiguously demonstrated that zinc was active against both antibiotic-resistant propionibacteria and fully sensitive strains. The reference showed that in 55

propionibacterial strains, isolated from acne patients, the MIC of zinc acetate was the same irrespective of whether the bacteria were antibiotic-sensitive or antibiotic-resistant. Furthermore, the authors recognised that zinc had a positive role to play in the treatment of acne patients where both antibiotic-sensitive and antibiotic-resistant bacteria were present. This was highlighted in the summary where the authors stated that 'It is recommended that these agents [azelaic acid, benzoyl peroxide and zinc acetate] are prescribed either concomitantly with, or immediately following, courses of oral or topical antibiotics for acne in order to minimise the selection and dissemination of antibiotic-resistant strains of propionibacteria'.

Yamanouchi stated that the use of this data, therefore, to support the claim was not ambiguous and did not constitute a breach of Clause 7.2.

Yamanouchi stated that, in addition, the use of Farmery *et al* to support the claim was not misleading. Doctors were fully aware of the extensive use of *in vitro* work in any discussion on, or reference to, antibiotic sensitivities. MCS (microscopy, culture, sensitivity) tests were routinely requested by GPs in order to find out to which antibiotics a given pathogen was sensitive. GPs, on average, would request somewhere in the order of one test per day. The sensitivity of propionibacteria to antibiotics, in this reference, was tested in agar plates in a comparable manner to that of a routine MCS test.

Yamanouchi stated that the use of this *in vitro* work, therefore, was not misleading to doctors, as they would be fully aware that the sensitivity of bacteria to

any agent was carried out in the laboratory.

In conclusion, Yamanouchi did not consider that the claim was ambiguous because the cited references clearly demonstrated that zinc was active against antibiotic-resistant and fully sensitive bacteria. Nor did the company consider that the claim was misleading, since the majority of GPs would be fully aware that any bacterial sensitivity tests were carried out *in vitro*. Yamanouchi considered that the claim that zinc was active against both antibiotic-resistant propionibacteria and fully sensitive strains did not constitute a breach of Clause 7.2.

PANEL RULING

The Panel noted its comments about the study by Farmery *et al* made in its ruling in point 1 above and also its comments regarding the use of *in vitro* data. The Panel accepted that doctors would be aware that antibiotic sensitivity tests were performed *in vitro* but noted that in this case Farmery *et al* had stated that it was yet to be determined whether its results would be seen during *in vivo* use. The Panel considered that in the circumstances readers should have been made aware that similar data had yet to be generated *in vivo*. The Panel considered that the claim was misleading as alleged. A breach of Clause 7.2 was ruled.

Complaint received **17 January 2001**

Case completed **1 March 2001**

HEALTH AUTHORITY PRESCRIBING MANAGER v MERCK PHARMACEUTICALS

Alcoholism awareness campaign

A health authority prescribing manager complained about an advertisement which had appeared in a national newspaper as part of an alcoholism awareness campaign conducted by Merck Pharmaceuticals. The advertisement in question was headed 'Alcoholics will go to any lengths to hide their habit'. This was followed by an illustration of three bottles labelled 'Top of the wardrobe', 'Behind the toilet' and 'Under the bed'. The text of the advertisement included the statement 'If you have just realised that drink has too strong a hold over you, help is near at hand. There are medicines available on prescription that can reduce your craving for alcohol and help break your drinking pattern'. Reference was made to phoning '... your doctor's surgery or local alcohol services and make an appointment right now'. The bottom of the advertisement stated that it was sponsored by Merck Pharmaceuticals and the company's website address was provided. The campaign included two other similar advertisements.

The complainant stated that whilst not directly advertising to the public, the advertisement must surely breach the Code. The advertisement was in the same format as those of the Samaritans and so could be construed as such. It inferred that the alcoholic could go to his general practitioner and be given a prescription. Merck made such a medicine.

The Panel considered that patient education programmes were a legitimate activity for a pharmaceutical company to undertake provided that such programmes were in accordance with the Code. Such activities might facilitate the market development of the sponsoring company's products but this was not necessarily in breach of the Code. Each case had to be judged on its merits.

The Panel noted that Merck's product, Campral EC, was indicated for therapy to maintain abstinence in alcohol dependent patients. It should be combined with counselling. It did not constitute treatment for the withdrawal period. Treatment with Campral EC should only be initiated after weaning therapy, once the patient was abstinent from alcohol.

The Panel noted that a website address was included on the advertisement. The home page of the website was headed 'Merck Pharmaceuticals in the UK' and included a number of links. The description 'Products and Services' linked to a page which listed a number of therapeutic areas including CNS. The brand and generic names of the Merck products in each therapeutic area were given; the indications were not. The CNS section listed Campral, Gamanil and Optimax. The page included a number of links; clicking on the product name gave direct access to the relevant summary of product characteristics (SPC) while 'Other Merck websites' led to a link to Alcowebe which was described as 'Expanding awareness and understanding of alcohol disease through the Internet'.

One of the requirements of the Code was that statements must not be made for the purpose of encouraging members

of the public to ask their doctors to prescribe a specific medicine. The Panel noted that none of the three newspaper advertisements used mentioned specific medicines. In the Panel's view the website architecture was a relevant factor. In this instance the reference to the Merck website with the subsequent link to the SPC for Campral EC was not unreasonable. The Panel noted the Code allowed SPCs to be provided to the public on request. SPCs could be placed on open access websites.

The Panel considered that the advertisement would increase public awareness of alcoholism and encourage people to discuss possible treatment options with their general practitioner or contact local alcohol services. This was not necessarily unacceptable. Patients were not being encouraged to ask their doctors specifically for the Merck product. The Panel noted that there were a number of different treatments available including Merck's product, not all of which were medicines. Patients visiting their doctors as a result of seeing the campaign would not necessarily be prescribed a Merck product. Patients had to be abstinent from alcohol before therapy with Campral EC could be initiated.

The Panel did not consider that the materials constituted an advertisement to the general public of a prescription only medicine. While acknowledging that there was a fine distinction between education and promotion, the Panel did not consider that the information given was such as to encourage patients to request a specific medicine. No breach of the Code was ruled.

The Panel noted that the Code required that 'Promotional material must not imitate the ... copy, slogans or general layout adopted by other companies in a way which is likely to mislead or confuse'. The Panel examined the five Samaritan advertisements provided. The Panel considered that although there were similarities between them these were not such as to confuse or mislead the reader. No breach of the Code was ruled in that regard.

A health authority prescribing manager complained about an advertisement (reference ZZ10255) placed by Merck Pharmaceuticals in The Times, 13 January.

The advertisement was headed 'Alcoholics will go to any lengths to hide their habit'. This was followed by an illustration of three bottles labelled 'Top of the wardrobe', 'Behind the toilet' and 'Under the bed'. The text of the advertisement included the statement 'If you have just realised that drink has too strong a hold over you, help is near at hand. There are medicines available on prescription that can reduce your craving for alcohol and help break your drinking

pattern'. Reference was made to phoning '... your doctor's surgery or local alcohol services and make an appointment right now'. The bottom of the advertisement stated that it was sponsored by Merck Pharmaceuticals and the company's website address was provided.

One of Merck's products, Campral EC, was indicated as therapy to maintain abstinence in alcohol dependent patients. It should be combined with counselling.

COMPLAINT

The complainant stated that whilst not directly advertising to the public, the advertisement must surely breach the Code. The complainant also stated that the advertisement was in the same format as those of the Samaritans and so could be construed as such. It inferred that the alcoholic could go to his general practitioner and be given a prescription. The complainant pointed out that Merck made such a medicine.

RESPONSE

Merck explained that there were three advertisements which had appeared in various national newspapers. Merck submitted that the advertisements were intended to gain the attention of people who knew they had a serious alcohol problem and who wanted to try and overcome it. The advertisement stated that help was available; medicines were available on prescription that could reduce the craving for alcohol and help break their drinking pattern; their doctor could help them; they should make an appointment with their doctor or local alcohol clinic.

The advertisement was therefore intended to encourage those seeking help in dealing with their alcoholism, and those whose lives were affected by alcoholics. It did not advertise a particular prescription medicine to the public, either directly or by inference, although it did refer to medicines being available to help in the treatment of alcoholism. The intention was to provide some reassurance that in addition to the perception of most people regarding the treatment of alcoholism, ie withdrawal from alcohol and counselling, there were also medicines available which would help in the entire process. Although a member of the public might not be aware of the availability of any particular medicinal products, these ranged from the use of chlordiazepoxide (Librium), diazepam (Valium) or chlormethiazole (Heminevrin) to reduce craving by the relief of acute alcohol withdrawal symptoms in the short term, to the use of acamprosate (Campral EC) and disulfiram (Antabuse) to help reduce the craving and break the drinking pattern longer term.

Although the advertisement was paid for by Merck there was no reference to its product, Campral EC, either by brand name, generic name or by a specific indication. A reference to Merck's website was included in the advertisement; however, this contained no promotional materials and no reference to products for treating alcohol-related conditions. A link to the summary of product characteristics (SPC) for Campral was included; however this was under a

heading of 'CNS', together with two products for treating depression. Under a separate link to 'other Merck websites' access could be gained to the 'Alcoveb' site which provided general information on alcohol and dependency problems. Alcoveb was managed by an independent editorial board and was partly financed by the European Commission. Merck submitted that as could be seen from the initial page of the Alcoveb site and the 'Glossary' and 'Frequently asked Questions', this provided no product-specific information. Copies of the relevant pages from the website and links were provided.

Merck submitted that the inclusion of website addresses on all types of communication was now commonplace, even on letterheads, and in this instance the only information accessible to the public from its website was non-promotional and available to the public in other forms, for example in the ABPI Compendium of Summaries of Product Characteristics and Data Sheets. The advertisements did not therefore contravene Clauses 20.1 or 20.2 of the Code as no prescription only medicines were being advertised to the public, the public only being encouraged to seek help from their doctors. The information included in the advertisement, either directly or indirectly via the website address, was strictly factual, and did not raise unfounded hopes of successful treatment or mislead with respect to safety. The advertisement did not encourage the public to ask their doctors to prescribe a specific product.

With regard to the allegation that the advertisement was in the same format as those of the Samaritans and so could be construed as such, Merck had obtained copies of what it understood were the five most recent advertisements used by the Samaritans which were launched in December 2000. Of these five advertisements, one was text only and two others were colour advertisements with minimal text stating 'You don't have to deal with it all by yourself', and the Samaritans logo. The remaining two advertisements were apparently black and white and featured a cartoon character and mixed font text. Other than the fact that Merck's advertisements used a distinct bold type which was intended to produce a significant contrast to the surrounding text, there appeared to be little similarity between Merck's advertisements and any of those of the Samaritans.

Merck did not therefore believe that the advertisement imitated the devices, copy slogans or general layout adopted by the Samaritans or any other organisation. It was made clear in the advertisements that they were sponsored by Merck.

PANEL RULING

The Panel considered that patient education programmes were a legitimate activity for a pharmaceutical company to undertake provided that such programmes were in accordance with the Code. Such activities might facilitate the market development of the sponsoring company's products but this was not necessarily in breach of the Code. Each case would need to be judged on its merits.

The Panel noted that Clause 20.1 prohibited the advertising of prescription only medicines to the

general public. Clause 20.2 of the Code permitted information to be supplied directly or indirectly to the general public but such information had to be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their doctor to prescribe a specific medicine.

The Panel noted that the advertisement in question referred to the availability of medicines on prescription that could reduce the craving for alcohol and help break the drinking pattern. No specific medicine was mentioned in the advertisement.

The Panel noted that the SPC for Campral EC stated that the product was indicated for therapy to maintain abstinence in alcohol dependent patients. It should be combined with counselling. Campral EC did not constitute treatment for the withdrawal period. Treatment with Campral EC should only be initiated after weaning therapy, once the patient was abstinent from alcohol.

The Panel noted that a website address was included on the advertisement. The home page of the website was headed 'Merck Pharmaceuticals in the UK' and included a number of links. The description 'Products and Services' linked to a page which listed the following therapeutic areas: Cardiovascular, Women's Health, CNS, Others, Devices and Merck Consumer Healthcare. The brand and generic names of the Merck products in each therapeutic area were given; the indications were not. The CNS section listed Campral, Gamanil and Optimax. The page included a number of links; clicking on the product name gave direct access to the relevant SPC while 'Other Merck websites' led to a link to Alcobeb which was described as 'Expanding awareness and understanding of alcohol disease through the Internet'.

The Panel noted that one of the requirements of Clause 20.2 of the Code was that statements must not be made for the purpose of encouraging members of the public to ask their doctors to prescribe a specific medicine. The Panel noted that none of the advertisements mentioned specific medicines. In the Panel's view the website architecture was a relevant factor. In this instance the reference to the Merck website with the subsequent link to the SPC for Campral EC was not unreasonable. The Panel noted that the supplementary information to Clause 20.2 of the Code stated that, *inter alia*, SPCs could be provided to the public on request. The guidance on the Internet published in the Code of Practice Review stated that SPCs could be placed on open access websites.

The Panel considered that the advertisement would increase public awareness of alcoholism and encourage people to discuss possible treatment options with their general practitioner or contact local alcohol services. This was not necessarily unacceptable. Patients were not being encouraged to ask their doctors specifically for the Merck product. The Panel noted that there were a number of different treatments available including Merck's product, not all of the treatments were medicines. Patients visiting their doctors as a result of seeing the campaign would not necessarily be prescribed a Merck product. Patients had to be abstinent from alcohol before therapy with Campral EC could be initiated. In the Panel's view patients consulting the website were not being encouraged to ask their doctors specifically for the Merck product.

The Panel did not consider that the materials constituted an advertisement to the general public of a prescription only medicine and no breach of Clause 20.1 of the Code was ruled.

The Panel, while acknowledging that there was a fine distinction between education and promotion, did not consider that the information given was such as to encourage patients to request a specific medicine. No breach of Clause 20.2 of the Code was ruled.

The Panel noted that Clause 9.3 stated, *inter alia*, that 'Promotional material must not imitate the ... copy, slogans or general layout adopted by other companies in a way which is likely to mislead or confuse'. The Panel examined the five Samaritan advertisements provided. One asked the question 'Do you think about leaving a party the moment you arrive?' beneath a picture of a dejected cartoon character. A second advertisement asked 'Would you feel more comfortable sitting under your desk rather than on it?' above a cartoon image of a man beneath a desk. The Samaritans' logo and telephone number appeared at the bottom of each advertisement; the website address was printed along the outside edge. The Panel considered that the design and layout of the other three advertisements was wholly dissimilar to that at issue.

The Panel considered that although the typeface in both the Merck and Samaritan advertisements was eye catching and varied throughout in size and boldness, the similarities between them were not such as to confuse or mislead the reader. No breach of Clause 9.3 was ruled.

Complaint received 12 February 2001

Case completed 7 March 2001

HEAD OF PRESCRIBING AND MEDICINES MANAGEMENT v JANSSEN-CILAG and ORGANON LABORATORIES

Risperdal leaflet and tablet recognition leavepiece

The head of prescribing and medicines management at a health authority complained about the promotion of Risperdal (risperidone) by Janssen-Cilag and Organon Laboratories.

The complainant noted the recent warning from the Committee on Safety of Medicines (CSM) informing practitioners that thioridazine was now only licensed for second line use in schizophrenia. As a result of this there were a significant number of elderly patients who were receiving thioridazine for what were now unlicensed indications, such as agitation and aggression. These patients would have to have their treatment reviewed, gradually withdrawn and if appropriate changed to an alternative medication. The health authority had worked to provide sound evidence-based advice to general practitioners on the licensed options available to their patients. However, it had been reported that Janssen-Cilag representatives had been promoting Risperdal as an alternative to thioridazine for elderly, agitated patients. The complainant noted that Risperdal was not licensed for calming elderly, agitated patients. It was only licensed for acute and chronic schizophrenic psychoses and other psychotic conditions. There was a clear inference in material which had been circulated to general practitioners that Risperdal might be used as an alternative to thioridazine for unlicensed indications. This material consisted of a tablet recognition leavepiece, the front of which stated 'Risperdal is effective in aggressive, agitated elderly patients' and a leaflet which suggested switching to Risperdal. The first paragraph on the third page of the leaflet was misleading; it appeared to suggest that the CSM was advising a switch to Risperdal: 'If switching to Risperdal from thioridazine reduce the dose over one to two weeks, as advised by the CSM'.

The Panel noted that prior to the CSM warning thioridazine had been used to treat: schizophrenia; anxiety, agitation and restlessness in the elderly; moderate to severe psychomotor agitation; violent and dangerously impulsive behaviour; mania/hypomania; behavioural disorders and epilepsy in children. Its use was now restricted to the second line treatment of schizophrenia in adults. Prior to the CSM warning thioridazine data sheets had included a specific dosage recommendation for the treatment of 'anxiety, agitation and restlessness in the elderly: 30-100mg' as a distinct dosage recommendation from its use in patients with schizophrenia (150-600mg).

Risperdal was indicated for the treatment of acute and chronic schizophrenic psychoses, and other psychotic conditions in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility and suspiciousness) and/or negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) were prominent. Risperdal also alleviated affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia. In contrast to the previous

licence for thioridazine, Risperdal had no licensed non-antipsychotic use.

The leavepiece had been previously considered in Cases AUTH/1116/1/01 and AUTH/1118/1/01. It dealt solely with Risperdal and its purpose was to show health professionals what the various presentations and formulations of the product looked like. The strapline 'From psychotic to cool, calm and collected' was at the top of the leavepiece and the claim 'Risperdal is effective in aggressive, agitated elderly patients' was beneath it. The Panel considered that whilst the claim did not refer to psychoses in the elderly, it would be read in the light of the strapline at the top of the leavepiece. The leavepiece had not been distributed with material referring to the restrictions on the prescription of thioridazine; it was part of an earlier campaign. It did not refer to thioridazine and the treatment of 'anxiety, agitation and restlessness in the elderly', the symptoms that had been used in previous thioridazine data sheets when referring to the non-psychotic elderly. The Panel did not consider that the leavepiece inferred that Risperdal might be used as an alternative to thioridazine in non-psychotic elderly patients who were agitated. No breach of the Code was ruled.

The Panel noted that on page 1 of the leaflet was the statement 'By mid-March 2001 all patients on thioridazine should have been reviewed and some may need to be switched – but what to?'. Page 2 of the leaflet was headed with 'Where appropriate why not switch to Risperdal' beneath which was the claim 'Risperdal is effective in aggressive, agitated elderly patients suffering psychoses' and two other claims. Page 3 was headed 'Switching to Risperdal' beneath which was the statement 'If switching to Risperdal from thioridazine reduce the dose over one to two weeks, as advised by the CSM'. There then followed instructions of how to initiate Risperdal therapy and the Risperdal product logo. Running along the bottom of pages 2 and 3 in stylised, large, bold type was the strapline 'From psychotic to cool, calm and collected'.

The Panel noted that as thioridazine was an antipsychotic there was a possibility for confusion regarding its previous licensed non-psychotic use ie 'anxiety, agitation and restlessness in the elderly' and the use of Risperdal in psychoses. Some of the symptoms of schizophrenia and dementia were the same. Given the possibility of confusion the Panel considered that it would have been helpful if the leaflet had drawn a clear distinction between the previously licensed non-psychotic use of thioridazine and the licensed indications for Risperdal. The Panel noted, however, that the leaflet

referred to the use of Risperdal in 'aggressive, agitated elderly patients suffering psychoses' and that in relation to the rest of the leaflet the strapline 'From psychotic to cool, calm and collected' was prominent. There was no mention of 'anxiety, agitation and restlessness in the elderly' as there had been in previous thioridazine data sheets. On balance the Panel considered that the elderly patient population for whom Risperdal was a suitable alternative to thioridazine had been stated clearly enough. No breach of the Code was ruled in that regard.

The Panel noted that page 3 of the leaflet stated 'If switching to Risperdal from thioridazine reduce the dose over one to two weeks, as advised by the CSM'. A similar sentence had been considered in Cases AUTH/1114/1/01 and AUTH/1116/1/01 – AUTH/1120/1/01. As in the previous cases, the Panel considered that the sentence now in question was ambiguous. It could be read to mean that the CSM had given dosage instructions with regard to switching patients from thioridazine to Risperdal specifically whereas the CSM advice to reduce the dose of thioridazine over one to two weeks applied to the discontinuation of the medicine whatever the circumstances. The Panel noted that when advising doctors about the restrictions on the prescription of thioridazine, the CSM had not suggested any alternative therapy. The Panel considered that the leaflet was misleading as alleged in this regard and ruled a breach of the Code.

In the Panel's view the complainant had not made any allegations about the conduct of any specific representative; the complaint related to the material which representatives were leaving with doctors. No rulings were made with regard to representative activity.

The head of prescribing and medicines management at a health authority complained about the promotion of Risperdal by Janssen-Cilag Ltd. Janssen-Cilag co-promoted Risperdal (risperidone) with Organon Laboratories Ltd and the matter was taken up with both companies.

COMPLAINT

The complainant noted the recent warning from the Committee on Safety of Medicines (CSM) about thioridazine informing practitioners of changes in its licensed indications. Thioridazine was now only licensed for second line use in schizophrenia. As a result of this there were a significant number of elderly patients who were receiving thioridazine for what were now unlicensed indications, such as agitation and aggression. These patients would now be required to have their treatment reviewed, gradually withdrawn and if appropriate changed to an alternative medication.

The complainant stated that the health authority had worked to provide sound evidence-based advice to general practitioners on the licensed options available to their patients. However, it had been reported that Janssen-Cilag representatives had been promoting Risperdal as an alternative to thioridazine for elderly, agitated patients. The complainant noted that

Risperdal was not licensed for calming elderly, agitated patients. It was only licensed for acute and chronic schizophrenic psychoses and other psychotic conditions.

The complainant stated that there was a clear inference in material which had been circulated to general practitioners that Risperdal might be used as an alternative to thioridazine for unlicensed indications. This material consisted of a laminated card (ref 605450), which was a tablet recognition leaviepiece, the front of which stated 'Risperdal is effective in aggressive, agitated elderly patients' and a leaflet (ref 606272) which suggested switching to Risperdal. The first paragraph on page 3 of the leaflet was misleading; it appeared to suggest that the CSM was advising a switch to Risperdal: 'If switching to Risperdal from thioridazine reduce the dose over one to two weeks, as advised by the CSM'.

In the complainant's view this promotion was misleading and unacceptable and should be withdrawn.

RESPONSE

Janssen-Cilag responded on behalf of both itself and Organon Laboratories.

Janssen-Cilag noted that it had recently addressed an identical complaint regarding the laminated card (Case AUTH/1116/1/01) which the Panel had ruled not to be in breach of the Code. The company did not, therefore, propose to address this further.

With regard to the leaflet Janssen-Cilag stated that it was part of a short-term campaign and had been used by its sales team in its promotional activities in primary care and also as a mailing to primary care staff. Page one of the leaflet reminded doctors that all patients currently on thioridazine should be reviewed and that some of these might need to switch to an alternative medication. Page two suggested Risperdal as one alternative but only where appropriate.

Janssen-Cilag noted that the indication for thioridazine in the elderly was broad, symptom-based and rather non-specific. It was thus inevitable that a proportion of these patients treated with thioridazine under this broad indication would in fact be suffering from a psychotic condition and would have prominent psychotic symptoms in conjunction with or actually causing their symptoms of agitation and/or restlessness.

The first stab-point on page two clearly stated that Risperdal was effective in aggressive, agitated elderly patients suffering psychoses and was fully consistent with the Risperdal summary of product characteristics (SPC) which stated: 'Risperdal is indicated for the treatment of acute and chronic schizophrenic psychoses, and other psychotic conditions, in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility, suspiciousness), and/or negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) are prominent. Risperdal also alleviates affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia'.

In the SPC hostility or aggression was clearly identified as a positive symptom and Janssen-Cilag submitted that agitation was a very common sequelae of a psychotic state such that it would frequently accompany such a condition especially in the elderly. Thus the claim that Risperdal was effective in aggressive, agitated elderly patients within the context of psychosis was both accurate and legitimate.

Janssen-Cilag noted that the complainant further alleged that the statement on page 3, 'If switching to Risperdal from thioridazine reduce the dose over one to two weeks, as advised by the CSM' implied that the CSM was advising a switch to Risperdal. This was plainly not the case. The statement was structured as a conditional proposition related to an action with the suffix qualifying the action. The condition that had to be satisfied was that the doctor wished to switch to Risperdal; the consequent action was the reduction of thioridazine over one to two weeks; the qualification ie 'as advised by CSM' pertained solely to the action ie reduction of the dose of thioridazine. The construct of the sentence was clear and unambiguous and did not imply that the CSM advised a switch to Risperdal as alleged.

Janssen-Cilag did not accept that there had been a breach of Clause 3.2 or 7.2 of the Code.

PANEL RULING

The Panel noted that prior to the CSM warning thioridazine had been used to treat: schizophrenia; anxiety, agitation and restlessness in the elderly; moderate to severe psychomotor agitation; violent and dangerously impulsive behaviour; mania/hypomania; behavioural disorders and epilepsy in children. Following the CSM advice the use of thioridazine was now restricted to the second line treatment of schizophrenia in adults. The Panel noted that prior to the CSM warning thioridazine data sheets had included a specific dosage recommendation for the treatment of 'anxiety, agitation and restlessness in the elderly: 30-100mg' as a distinct dosage recommendation from its use in patients with schizophrenia (150-600mg) (ref ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1999-2000).

The Panel noted that Risperdal was indicated for the treatment of acute and chronic schizophrenic psychoses, and other psychotic conditions in which positive symptoms (such as hallucinations, delusions, thought disturbances, hostility and suspiciousness) and/or negative symptoms (such as blunted affect, emotional and social withdrawal, poverty of speech) were prominent. Risperdal also alleviated affective symptoms (such as depression, guilt feelings, anxiety) associated with schizophrenia. The Panel noted that, in contrast to the previous licence for thioridazine, Risperdal had no licensed non-antipsychotic use.

The Panel noted that the laminated card was a tablet recognition leavepiece. The leavepiece, together with a 'Dear Doctor' letter which addressed the issue of the recently introduced CSM restrictions on the prescription of thioridazine, had been considered in Cases AUTH/1116/1/01 and AUTH/1118/1/01. The front of the card was headed with the Risperdal

product logo beneath which was the strapline 'From psychotic to cool, calm and collected'. The claims 'Risperdal is effective in aggressive agitated elderly patients' and 'The starting dose is 0.5mg bd' appeared beneath the strapline. The bottom half of the card displayed photographs of the different presentations and formulations of Risperdal and included the claim 'A highly flexible range for the elderly'. The complainants had alleged that the leaflet seemed to suggest that Risperdal was a suitable alternative to the use of thioridazine to treat restlessness, wandering and agitation in the elderly.

In its response to the previous cases Janssen-Cilag stated that the leavepiece was part of an earlier campaign and had not been distributed with the 'Dear Doctor' letter. The leavepiece was primarily designed to highlight the availability of the recently introduced 0.5mg tablet and provided a visual identification aid to help health professionals differentiate it from other tablet strengths.

Janssen-Cilag had noted that at the top of the piece was the strapline 'From psychotic to cool, calm and collected'. The strapline was a prominent part of the piece being in a larger font size than the other text and stylised and emboldened to draw the reader's attention. The statement itself clearly denoted the movement from a psychotic condition (diagnosis invariably required prominent positive and/or negative psychotic symptoms) to a non-psychotic state (symptoms controlled and/or absent) and was therefore completely consistent with the licensed indication for Risperdal as stated in the SPC.

Janssen-Cilag stated that the subsequent and secondary claim regarding aggressive, agitated elderly patients had to be seen in the context of the overarching statement regarding psychosis as described above. The company noted that it immediately followed the strapline. Market research with primary care staff strongly suggested that GPs identified well with this terminology when allied to descriptions of symptomatology ie it was relevant to its intended audience. In the SPC hostility or aggression was clearly identified as a positive symptom and the company submitted that agitation was a very common sequelae of a psychotic state such that it would frequently accompany such a condition especially in the elderly. Thus the claim that Risperdal was effective in aggressive, agitated elderly patients within the context of psychosis was both accurate and legitimate. Janssen-Cilag stated that it had specifically chosen to highlight hostility (and agitation) here in the context of a psychotic illness as this often posed the most difficult management problems in primary care and was thus of particular relevance to the intended audience.

Panel Ruling in Cases AUTH/1116/1/01 and AUTH/1118/1/01 The Panel noted that the leavepiece dealt solely with Risperdal; its purpose was to show health professionals what the various presentations and formulations of the product looked like. There was no reference to any other product.

The strapline 'From psychotic to cool, calm and collected' was at the top of the leavepiece and the claim 'Risperdal is effective in aggressive, agitated

elderly patients' appeared beneath it. The Panel considered that whilst the claim did not refer to psychoses in the elderly it would be read in the light of the strapline at the top of the leavepiece.

The Panel noted Janssen-Cilag's submission that the leavepiece had not been distributed with the Risperdal letters referring to the restrictions on the prescription of thioridazine; it was part of an earlier campaign. The leavepiece did not refer to thioridazine and the treatment of 'anxiety, agitation and restlessness in the elderly', the symptoms that had been used in previous thioridazine data sheets when referring to the non-psychotic elderly. The Panel did not consider that the leavepiece was misleading as alleged. No breach of Clause 7.2 was ruled.

Cases AUTH/1128/1/01 and AUTH/1129/1/01 The Panel did not consider that the leavepiece inferred that Risperdal might be used as an alternative to thioridazine in non-psychotic elderly patients who were agitated. No breach of Clauses 3.2 and 7.2 was ruled.

The Panel noted on page 1 of the leaflet was the statement 'By mid-March 2001 all patients on thioridazine should have been reviewed and some may need to be switched – but what to?'. Page 2 of the leaflet was headed with 'Where appropriate why not switch to Risperdal' beneath which was the claim 'Risperdal is effective in aggressive, agitated elderly patients suffering psychoses'. Two other claims for Risperdal followed. Page 3 of the leaflet was headed 'Switching to Risperdal' beneath which was the statement 'If switching to Risperdal from thioridazine reduce the dose over one to two weeks, as advised by the CSM'. There then followed instructions of how to initiate Risperdal therapy and the Risperdal product logo. Running along the bottom of pages 2 and 3 in stylised, large, bold type was the strapline 'From psychotic to cool, calm and collected'.

The Panel noted that as thioridazine was an antipsychotic there was a possibility for confusion regarding its previous licensed non-psychotic use ie 'anxiety, agitation and restlessness in the elderly' and the use of Risperdal in psychoses. Some of the symptoms of schizophrenia and dementia were the same. Given the possibility of confusion the Panel considered that it would have been helpful if the leaflet had drawn a clear distinction between the

previously licensed non-psychotic use of thioridazine and the licensed indications for Risperdal. The Panel noted, however, that the leaflet referred to the use of Risperdal in 'aggressive, agitated elderly patients suffering psychoses' and that in relation to the rest of the leaflet the strapline 'From psychotic to cool, calm and collected' was prominent. There was no mention of 'anxiety, agitation and restlessness in the elderly' as there had been in previous thioridazine data sheets. On balance the Panel considered that the elderly patient population for whom Risperdal was a suitable alternative to thioridazine had been stated clearly enough. No breach of Clauses 3.2 and 7.2 of the Code was ruled in that regard.

The Panel noted that page 3 of the leaflet stated 'If switching to Risperdal from thioridazine reduce the dose over one to two weeks, as advised by the CSM'. A similar sentence had been considered in Cases AUTH/1114/1/01 and AUTH/1116/1/01 – AUTH/1120/1/01. In those cases the sentence read 'If you decide to change to Risperdal after re-evaluating your patients, reduce the dose of thioridazine over one to two weeks, as advised by the CSM'. As in the previous cases the Panel considered that the sentence now in question was ambiguous; it could be read to mean that the CSM had given dosage instructions with regard to switching patients from thioridazine to Risperdal specifically whereas the CSM advice to reduce the dose of thioridazine over one to two weeks applied to the discontinuation of the medicine whatever the circumstances. The Panel noted that when advising doctors about the restrictions on the prescription of thioridazine the CSM had not suggested any alternative therapy. The Panel considered that the leaflet was misleading as alleged in this regard and ruled a breach of Clause 7.2 of the Code.

In the Panel's view the complainant had not made any allegations about the conduct of any specific representative; the complaint related to the material which representatives were leaving with doctors. No rulings were made with regard to representative activity.

Complaint received **25 January 2001**

Case completed **6 March 2001**

PRIMARY CARE PHARMACIST v 3M HEALTH CARE

'Dear Pharmacist' letters about Airomir and Qvar

A primary care pharmacist complained about two 'Dear Pharmacist' letters sent by 3M Health Care. The first letter related to the Airomir Autohaler (CFC-free salbutamol) and stated 'You may not have heard about the recent discontinuation of a leading manufacturer's breath-actuated salbutamol pMDI. Your patients who currently use this brand will need to change at their next prescription'. The second letter related to Qvar (CFC-free beclomethasone) and stated 'You may not be aware of the recent discontinuation of a leading manufacturer's breath-actuated beclomethasone dipropionate (CFC-BDP) metered dose inhaler. Patients currently taking this brand may need to change at their next prescription'.

The complainant concerned the phrase 'recent discontinuation'. The complainant was aware that the 'Easibreathe' inhalers previously marketed under the Ventolin brand by Glaxo/Allen & Hanburys had been returned to their marketing authorization holder, Baker Norton, and that the supply would continue under the Salamol brand name, the product being unchanged. Likewise a similar situation would apply to the Becotide products which would become Beclazone brand.

The complainant was therefore surprised when he received the letters which, although not explicit in naming these products, implicitly named them, as they were the only main line alternatives to the 3M Health Care brands in this therapeutic field. The letters were erroneous in that the products had not been discontinued, they had solely changed names as the complainant was assured, before and after receiving the letters, by Baker Norton.

The complainant suggested that the clarity and transparency of the wording in the letters left a lot to be desired. He also believed that the letters represented the worst sort of attempted market manipulation with blatant misrepresentation and deception.

The Panel noted the submission from 3M Health Care that it could not refer by brand name to the products which had been withdrawn as Clause 7.10 of the Code prevented the use of other companies' brand names unless prior consent had been obtained. This had complicated matters. Baker Norton's 'Dear Healthcare Professional' letter about the matter was headed 'Easi-Breathe name changes in the UK' and stated that Baker Norton would be resuming responsibility for marketing Easi-Breathe in the UK, listed the changes to the Easi-Breathe brand names and stated that, *inter alia*, the dose, strength and pack size would remain the same. The Ventolin Easi-Breathe brand and the Becotide Easi-Breathe brand range had been discontinued. The Panel noted that the medicines and device remained available as Salamol Easi-Breathe and Beclazone Easi-Breathe from Baker Norton. The products, according to the complainant, were unchanged and had not been discontinued; they had solely changed their brand names.

The Panel considered that the letters at issue failed to reflect the situation. It was too simplistic to state that the products had been discontinued. The products still existed but had

been given new brand names. The position had not been made sufficiently clear. Each letter was ruled in breach of the Code.

A primary care pharmacist complained about two 'Dear Pharmacist' letters sent out by 3M Health Care Limited.

The first letter (ref 0101/A1/002/016) related to the Airomir Autohaler (CFC-free salbutamol sulphate). Under the heading 'The right recommendation?', it stated 'You may not have heard about the recent discontinuation of a leading manufacturer's breath-actuated salbutamol pMDI. Your patients who currently use this brand will need to change at their next prescription'.

The second letter (ref 0101/QV/004/048) related to Qvar (CFC-free beclomethasone dipropionate). Under the heading 'A change for the better', it stated 'You may not be aware of the recent discontinuation of a leading manufacturer's breath-actuated beclomethasone dipropionate (CFC-BDP) metered dose inhaler. Patients currently taking this brand may need to change at their next prescription'.

COMPLAINT

The complainant stated that the letters had been sent to all primary care pharmacists and he believed that they infringed the Code.

The complaint centred on the use of the phrase 'recent discontinuation'. As a primary care pharmacist who sat on the prescribing sub-committee of his local primary care group, he attempted to keep up to date on all product changes. The complainant was aware that the 'Easibreathe' inhalers previously marketed under the Ventolin brand by Glaxo/Allen & Hanburys had been returned to their marketing authorization holder, Baker Norton, and that the supply would continue under the Salamol brand name, the product being unchanged. Likewise he recognised that a similar situation would apply to the Becotide products which would become Beclazone brand.

The complainant was therefore surprised when he received the 3M Health Care letters which, although not explicit in naming these products, implicitly named them, as they were the only main line alternatives to the 3M Health Care brands in this therapeutic field. The letters were erroneous in that the products had not been discontinued, they had solely changed names as the complainant was assured, before and after receiving the letters, by his Baker Norton representative and its marketing department. As this was the complainant's local practice's preferred brand and it, and all the main local pharmacies which served the practice, had an agreement on matters of inhaler policy, including CFC switch and preferred products, these letters were disturbing.

The complainant had raised the matter with 3M Health Care; however it seemed reluctant to comment on this matter and would have the complainant believe that the switch of brand name constituted a discontinuation.

The complainant suggested that the clarity and transparency of the wording in the letters left a lot to be desired. He also believed that the letters represented the worst sort of attempted market manipulation with blatant misrepresentation and deception.

When writing to 3M Health Care the Authority drew attention to Clause 7.2 of the Code.

RESPONSE

Letter on Airomir

3M Health Care noted that the complainant referred specifically to the use of the phrase 'recent discontinuation' and stated that 3M Health Care was inaccurate in claiming that a leading manufacturer's breath-actuated salbutamol pMDI was discontinued. The complainant had correctly identified that the product referred to was Allen & Hanburys' brand of Ventolin Easi-Breathe. 3M Health Care did not use the brand name in the promotional item in keeping with Clause 7.10 of the Code.

It was 3M Health Care's understanding that branded Ventolin Easi-Breathe, distributed and branded by Allen & Hanburys, was no longer available. Baker Norton had resumed responsibility for marketing Easi-Breathe in the UK in that it had taken over the responsibility for the sales and marketing of the inhalation device, Easi-Breathe. The device was being used to deliver the drug, Salamol. The branded medicine Ventolin was still a trade mark of Allen & Hanburys, to 3M Health Care's knowledge. Thus, Allen & Hanburys' branded Ventolin Easi-Breathe breath-actuated product was effectively discontinued.

A mailing on the subject by Baker Norton which was provided clearly specified that the brands were not interchangeable by pharmacists or dispensers when filling a prescription. Another item from Baker Norton, also provided, detailed important information about Easi-Breathe and clearly implied, as had been highlighted in the 3M Health Care letter, that the patient prescription would be changed as a result.

The letter from 3M Health Care stated 'Your patients who currently use this brand will need to change at their next prescription'. This information was accurate and did not mislead the health professional. Patients who were on Ventolin Easi-Breathe would no longer be able to receive the branded product and prescribers would be unable to prescribe Ventolin Easi-Breathe by brand. 3M Health Care was all too aware of patients' concerns when they were switched to different medicines without due consideration. In this case pharmacists would be required to explain the change to patients. 3M Health Care therefore contended that the branded drug-device combination was effectively discontinued and that the phrase 'recent discontinuation' was not misleading and not in breach of Clause 7.2.

Letter on Qvar

3M Health Care noted that the complainant referred specifically to the use of the phrase 'recent discontinuation' and stated that 3M Health Care was inaccurate in claiming that a leading manufacturer's breath-actuated beclomethasone dipropionate (CFC-BDP) metered dose inhaler was discontinued. The complainant had correctly identified that the products referred to were Allen & Hanburys' brands of CFC-BDP Easi-Breathe, namely Becloforte and Becotide Easi-Breathe. 3M Health Care did not use the brand names in the promotional item in keeping with Clause 7.10.

It was 3M Health Care's understanding that branded Becotide and Becloforte Easi-Breathe products manufactured by Allen & Hanburys were no longer available. Baker Norton had resumed responsibility for marketing Easi-Breathe in the UK in that it had taken over the responsibility for the sales and marketing of the inhalation device, Easi-Breathe. The device was being used to deliver the drug Beclazone. The branded medicines, Becloforte and Becotide, were still trade marks of Allen & Hanburys, to 3M Health Care's knowledge. These Allen & Hanburys' branded breath-actuated (Becotide and Becloforte Easi-Breathe) products were effectively discontinued.

A mailing on the subject by Baker Norton which was provided clearly specified that the brands were not interchangeable by pharmacists or dispensers when filling a prescription. Another item from Baker Norton, also provided, detailed important information about Easi-Breathe and clearly showed, as had been highlighted in the 3M Health Care letter, that the patient prescription would be changed as a result.

The letter from 3M Health Care stated 'Patients currently taking this brand may need to change at their next prescription'. This information was accurate and did not mislead the health professional. Patients who were on Becotide and Becloforte Easi-Breathe would no longer be able to receive the branded products and prescribers would be unable to prescribe Becotide and Becloforte Easi-Breathe by brand. 3M Health Care was all too aware of patients' concerns when they were switched to different medicinal products without due consideration. In this case pharmacists would be required to explain the change to patients. 3M Health Care therefore contended that the branded drug-device combination products were effectively discontinued and that the phrase 'recent discontinuation' was not misleading and not in breach of Clause 7.2.

3M Health Care was surprised at the allegation by the pharmacist that the letters by 3M Health Care represented 'the worst sort of attempted market manipulation with blatant misrepresentation and deception'. It strongly repudiated the allegation. The letter from 3M Health Care highlighted that patients' inhalation medication would need to be changed in view of the discontinuation of Ventolin, Becloforte and Becotide Easi-Breathe products and promoted the 3M Health Care respiratory brands as credible, cost-efficient, alternative breath-actuated products. The letters from Norton Healthcare, which had been provided, highlighting the change in patients' inhalation treatment were, in principle, equally

informative for its products, as were the letters from 3M Health Care and, in 3M Health Care's opinion, were not attempts at market manipulation or deception. 3M Health Care noted that the pharmacist had not interpreted the letters from Norton Healthcare in a negative light.

3M Health Care stated that it was never its intention to mislead healthcare professionals and it endeavoured to work within the Code when dealing with members of the health professions.

PANEL RULING

The Panel noted the submission from 3M Health Care that it could not refer by brand name to the products which had been withdrawn as the brand names of other companies' products could not be used unless prior consent had been obtained (Clause 7.10 of the Code). This had complicated matters.

The Panel examined the 'Dear Healthcare Professional' letter produced by Baker Norton about the matter and provided by 3M Health Care. The letter was headed 'Easi-Breathe name changes in the

UK' and stated that Baker Norton would be resuming responsibility for marketing Easi-Breathe in the UK, listed the changes to the Easi-Breathe brand names and stated that, *inter alia*, the dose, strength and pack size would remain the same. The Ventolin Easi-Breathe brand and the Becotide Easi-Breathe brand range had been discontinued.

The Panel noted that the medicines and device remained available as Salamol Easi-Breathe and Beclazone Easi-Breathe from Baker Norton. The products, according to the complainant, were unchanged and had not been discontinued; they had solely changed their brand names.

The Panel considered that the letters at issue failed to reflect the situation. It was too simplistic to state that the products had been discontinued. The products still existed but had been given new brand names. The position had not been made sufficiently clear. Each letter was ruled in breach of Clause 7.2 of the Code.

Complaint received **14 February 2001**

Case completed **23 March 2001**

CASE AUTH/1138/2/01

GENERAL PRACTITIONER v SHIRE

Promotion of Calcichew-D₃ Forte

A general practitioner complained that Shire was misleadingly marketing Calcichew-D₃ Forte (calcium and vitamin D₃) for the prevention of osteoporosis, an indication for which the product had no licence. The phrase 'for the prevention of osteoporosis' was repeated a number of times by one of the company's representatives and was clearly an essential part of her presentation. The complainant noted that the licensed indications for Calcichew-D₃ Forte were the treatment and prevention of vitamin D/calcium deficiency and also as an adjunct to specific therapy for osteoporosis. There was no mention of the prevention of osteoporosis within the product licence.

The Panel noted that the detail aid contained a flow diagram which showed that sub-optimal calcium and vitamin D levels would lead to osteoporosis and an increased risk of fracture. While the prevention of osteoporosis would be a potential benefit of Calcichew-D₃ Forte therapy in patients who had or might be susceptible to calcium/vitamin D deficiency, it was not a licensed indication for the product. In patients with osteoporosis who also required supplementation of calcium and vitamin D, Calcichew-D₃ Forte could be used as an adjunct to specific osteoporosis therapies.

A chart in the detail aid entitled 'Osteoporosis therapy options' listed Calcichew-D₃ Forte as one of the options. Two claims in the detail aid, and one in a booklet entitled 'Hip fractures and the role of calcium and vitamin D supplements', referred to the use of calcium and vitamin D as a treatment for osteoporosis. The Panel considered that both the detail aid and the booklet implied that Calcichew-D₃ Forte was licensed

in its own right as a specific medicine for the treatment of osteoporosis which was not so. A breach of the Code was ruled.

With regard to the representatives' training material, a slide set on osteoporosis contained some slides headed 'The prevention of osteoporosis and fracture'; one of these slides referred to calcium and vitamin D supplements reducing the risk of hip fracture. A slide set which instructed representatives on how to sell Calcichew-D₃ Forte also referred to the prevention of hip fracture. Nowhere in either slide presentation was it stated that Calcichew-D₃ Forte was only licensed in osteoporosis as adjunctive therapy. The Panel considered that the training material implied that Calcichew-D₃ Forte was licensed in its own right for the prevention of osteoporosis which was not so. A further breach of the Code was ruled.

A general practitioner complained about the promotion of Calcichew-D₃ Forte (calcium and vitamin D₃) by Shire Pharmaceuticals Ltd. The complainant wrote direct to Shire, copying his letter to the Authority.

COMPLAINT

The complainant thought that the representative had presented her promotional talk competently, clearly and professionally. The complainant stated that his complaint was not against her, nor against her presentation of the product, but specifically against a

misleading marketing of the product. From the outset of the presentation the complainant was informed that the product was being promoted 'for the prevention of osteoporosis'. This phrase was repeated a number of times within the product presentation and was clearly an essential part of the presentation which had been taught to the representative.

Since it was a relatively new product, at least in terms of its usage in primary care, and since the complainant had seen a few patients recommended this product by rheumatologists, he was interested to learn more and as the presentation progressed he asked what the licensed indications were. The reason that he was interested in this question was that often within a licence indication there was a guide as to how the condition might be defined.

Much to his shock and surprise, when he saw the summary of product characteristics (SPC) he read very clearly under section 4.1 that the licensed indication for the product was in the treatment and prevention of vitamin D/calcium deficiency. The second specific licensed indication was for its use as an adjunct to specific therapy for osteoporosis.

Specifically there was no mention of the prevention of osteoporosis within the product licence.

The complainant thought that the representative was as shocked and surprised to learn this as he was.

Clearly as a doctor he accepted that there were links between vitamin D/calcium deficiency and osteoporosis. Nevertheless he felt that the marketing of this product 'for the prevention of osteoporosis' was specifically dishonest, misleading and outside the licensed indications.

The complainant was notifying the Authority as he considered this to be a fairly clear breach of the Code.

RESPONSE

Shire stated that in its promotional material and in the training of its medical representatives, it had endeavoured to adhere to a combination of its licensed therapeutic indications for Calcichew-D₃ Forte, namely: the treatment and prevention of vitamin D/calcium deficiency (characterised by raised serum alkaline phosphatase levels associated with increased bone loss, raised levels of serum parathyroid hormone (PTH) and lowered 25-hydroxyvitamin D) particularly in the housebound and institutionalised elderly subjects, and the supplementation of vitamin D and calcium as an adjunct to specific therapy for osteoporosis, in pregnancy, in established vitamin D dependent osteomalacia and in other situations requiring therapeutic supplementation of malnutrition.

To maintain consistency with these indications, it had emphasised the well-documented logical progression of events (as in a flow chart in the detail aid) that led from calcium and vitamin D deficiency (treatable with Calcichew-D₃ Forte) to raised PTH, poor bone health and osteoporosis. There was ample evidence from several large well-conducted studies that calcium/vitamin D therapy improved bone health and reduced morbidity. Shire did not instruct its representatives to promote the product for the 'prevention of osteoporosis', as alleged.

1 Definition of 'therapy'

With reference to the SPC, the term 'therapy' in the context of osteoporosis was widely taken to include prevention and treatment of this condition, which was widespread and progressive in post-menopausal women. Therapy for osteoporosis included the treatment and prevention of vitamin D/calcium deficiency which was recommended as an adjunct to specific therapy. Hormone replacement therapy (HRT) was one of these specific therapies which were widely employed for the prevention of osteoporosis. Other therapies to which Calcichew-D₃ Forte might be used as an adjunct were: bisphosphonates, selective estrogen receptor modulators (SERMS) and lifestyle advice. Shire clearly identified these various 'osteoporosis therapy options', including Calcichew-D₃ Forte, in its detail aid.

The Royal College of Physicians in its Clinical Guidelines for the Prevention and Treatment of Osteoporosis (July 2000) stated 'In clinical practice this distinction between prevention and treatment [of osteoporosis] is less appropriate, since all agents currently in use act fundamentally in the same manner, ie by inhibition of bone resorption'. All these therapies acted to inhibit the otherwise relentless osteoporotic process which commenced for women at the menopause. Thereafter, loss of bone density was a continuous process in untreated patients and it was inappropriate on this continuum of disease progression that 'prevention' should suddenly become 'treatment' when a formal diagnosis of osteoporosis was made. In osteoporosis, clearly prevention and treatment merged into one – as a therapy.

2 Training programme

Copies of the following materials used in the training programme for Shire's medical sales representatives were provided:

- an 86-slide basic presentation to introduce the representatives to the therapeutic area and its therapy;
- a 10-slide presentation 'Guidelines for Osteoporosis in Coeliac and Inflammatory Bowel Disease';
- an 8-slide presentation of the 'Adoption Pathway' suggested for its use in the doctor interview;
- eleven publications of relevant clinical trials and review articles, nine of which incorporated a summary for the benefit of the representatives. It was emphasised to the representatives at the start of the training course that these summaries were for their perusal only and were not to be used in interviews with doctors.

In Shire's training and promotional materials, it described the deficiencies inherent in the osteoporotic condition and the various therapeutic options for prevention and treatment, one of which was calcium/vitamin D.

The rigorous training course undergone by Shire medical sales representatives for this product was initiated with an 86-slide presentation involving a lengthy description of the structure, function,

endocrinology and pathology of bone, leading on to a definition of osteoporosis, its causes, pathology, morbidity (particularly fractures), mortality and its therapy, including prevention and treatment. The importance of HRT and life-style advice as well as calcium and vitamin D supplementation was emphasised. In a 10-slide presentation on osteoporosis in coeliac and inflammatory bowel disease, a strategy for prevention and treatment of osteoporosis was developed, involving lifestyle advice and a variety of medical treatments including calcium and vitamin D. It was mentioned that such patients might well be calcium or vitamin D deficient and therefore might need calcium/vitamin D supplementation to correct this deficiency as part of their treatment (as per the SPC for Calcichew-D₃ Forte).

The background part of the training course was supplemented by copies of various clinical trial publications which supported the use of calcium/vitamin D supplementation in osteoporosis.

The 'Adoption Pathway', presented to the representatives at Shire's training course as a guide for the physician interview, described *inter alia* the suggested approach to a doctor who was not convinced of the role of Calcichew-D₃ Forte in preventing the relentless progression of the osteoporotic process. In this context the representative would use the detail aid to illustrate the role of Calcichew-D₃ Forte: firstly in managing sub-optimal calcium and vitamin D levels, the consequential secondary hyperparathyroidism and bone loss and secondly as one of several therapies for osteoporosis. Shire believed that this promotion was entirely within the licensed indications (see 3 below). Indeed, nowhere did Shire specifically direct its representatives to claim 'prevention of osteoporosis' but rather 'prevention and treatment of calcium/vitamin D deficiency' as one therapy for osteoporosis (see flow-chart in the detail aid).

3 Promotional material

Copies of Shire's detail aid, leavepiece and health needs assessment pack were presented. Shire drew attention to pages 6 and 10 of its detail aid, which it regarded as being particularly relevant to its arguments.

A theme was developed within the detail aid, which related sub-optimal levels of calcium and vitamin D to poor bone health. Treatment and prevention of these deficiencies could therefore treat and prevent osteoporosis. The representative led the complainant through this detail aid during the interview.

The therapy (treatment and prevention) of osteoporosis was aimed largely at elderly women (particularly the housebound and institutionalised) where calcium and vitamin D deficiency were common and osteoporosis occurred frequently, often with severe consequences. In such cases Calcichew-D₃ Forte treated calcium and vitamin D deficiency and as such helped to prevent and treat osteoporosis, as specified in the licence.

Shire referred particularly to page 6 of its detail aid, headed 'Where Calcichew-D₃ Forte fits in /

Osteoporosis Therapy Options', which displayed this medicine as one option to be used (particularly in the elderly where calcium and vitamin D deficiencies were common) concurrently with other therapies (including lifestyle advice). This item illustrated that Shire promoted the product as one of various options for therapy of this condition, entirely within the confines of the SPC. The representative in question, along with Shire's other representatives, adhered to this principle.

4 Response to complaint

It was alleged that Calcichew-D₃ Forte was promoted for the prevention of osteoporosis which, the complainant claimed, was specifically dishonest, misleading and outside the licensed indication. Shire entirely rejected this assertion on several counts.

- There was a strong link between calcium and vitamin D deficiency and osteoporosis (particularly in the housebound and institutionalised elderly, targeted in Shire's promotion) and therefore treatment and prevention of calcium/vitamin D deficiency (within the product licence) also acted as therapy (treatment and prevention) of osteoporosis. The complainant recognised in his letter of complaint that there were links between vitamin D/calcium deficiency and osteoporosis.
- The promotional material used by Shire's medical sales representatives presented the product as one of several options for therapy of osteoporosis, again within the licence.
- As could be seen from the training material, Shire's representatives were not trained to promote outside the licence. They utilised the vast amount of substantiated material available from the literature to support their promotional activities.
- Because of the relentless and progressive nature of untreated osteoporosis there was a 'blurring' of distinction between prevention and treatment of this condition, especially since it was not common to make the diagnosis on the formal definition involving bone mineral density via a scan. The Royal College of Physicians had recognised the limitation of this distinction (see 1 above).

5 Code of Practice

The Authority had requested that Shire bear in mind four clauses of the Code in its response:

Clause 3.2; for reasons described above, Shire believed that its promotion of Calcichew-D₃ Forte was in accordance with the marketing authorisation and was not inconsistent with the SPC.

Clause 7.2; Shire's comprehensive and scientifically accurate promotional material (see for example the detail-aid) contained information, claims and comparisons that were accurate, balanced, fair, objective and unambiguous and based on up-to-date evaluation of all evidence. Shire had not misled the audience, specifically with regard to 'therapy for osteoporosis'.

Clause 9.1; Shire had not promoted its product in a way likely to cause offence. In the large number of physician visits made regarding this product over more than four years, this was the first occasion that had provoked a complaint.

Clause 15.9; as described in detail above, Shire did not believe that its briefing material breached the Code in any way. Shire had not instructed its representatives to promote outside the licence.

6 Other items

Shire wished to point out that Calcichew-D₃ Forte was not a 'relatively new product' as stated by the complainant. It had been available since May 1996.

During the interview, the complainant did not permit the representative to present copies of clinical trial publications to support promotional claims. At the end of the interview, he would not accept copies of these trial publications, which she offered to leave.

In response to the Authority's question Shire confirmed that the representative had passed the ABPI medical representatives examination.

PANEL RULING

The Panel noted that Calcichew-D₃ Forte was licensed for the treatment and prevention of vitamin D/calcium deficiency particularly in the housebound and institutionalised elderly subjects. It was also licensed for the supplementation of vitamin D and calcium as an adjunct to specific therapy for osteoporosis, in pregnancy, in established vitamin D dependant osteomalacia and in other situations requiring therapeutic supplementation of malnutrition.

The Panel noted that page 10 of the detail aid headed 'The Consequences of Sub-Optimal Calcium and Vitamin D Levels' featured a flow diagram to show that sub-optimal calcium and vitamin D levels would lead to osteoporosis and an increased risk of fracture. The Panel noted that while the prevention of osteoporosis would be a potential benefit of Calcichew-D₃ Forte therapy, in those patients who either had or might be susceptible to calcium/vitamin D deficiency, it was not a licensed indication for the product. In those patients with osteoporosis who also required supplementation of calcium and vitamin D, Calcichew-D₃ Forte could be used as an adjunct to specific osteoporosis therapies. In the Panel's view not all patients with osteoporosis would need therapeutic supplementation of calcium and vitamin D. The Panel noted that therapies which were specifically licensed for osteoporosis included HRT, SERMs and bisphosphonates.

The Panel noted that page 6 of the detail aid (ref 003/0109) was headed 'Where Calcichew-D₃ Forte fits in'. The page featured a chart entitled 'Osteoporosis therapy options' which showed, according to age, which options should be employed when. One of the options listed was Calcichew-D₃ Forte, the others were SERMs, bisphosphonates, HRT and lifestyle advice. Page 14 of the detail aid headed 'Cost-effective treatment' featured the following quotation in a highlighted box 'The use of vitamin D with calcium in

elderly osteoporotic women saves resources and it is recommended that such individuals be offered such treatment'. The following page included the claim 'Calcium and vitamin D supplementation offers a cost-effective treatment for osteoporosis'.

Shire also provided a copy of a booklet entitled 'Hip fractures and the role of calcium and vitamin D supplements'. On page 37, under a heading of 'Osteoporosis treatment', it was stated that 'Calcium and vitamin D supplementation is probably the most appropriate treatment for elderly patients with hip fractures, as vitamin D deficiency and secondary hypoparathyroidism contribute to bone loss with advancing age'.

The Panel considered that both the detail aid and the booklet were misleading as they implied that Calcichew-D₃ Forte was licensed in its own right as a specific medicine for the treatment of osteoporosis. This was not so; the product was only licensed as an adjunct to specific therapy for osteoporosis. The Panel ruled breaches of Clauses 3.2 and 7.2 of the Code.

With regard to the representatives' training material, the Panel noted that slides 82 to 84 of the 86-slide set on osteoporosis were headed 'The prevention of osteoporosis and fracture'. Slide 85 was headed 'Where does calcium and vitamin D fit in?' The slide listed three bullet points, the final one of which was highlighted and read 'In elderly, mainly institutionalised people, the use of external hip protectors and taking calcium and vitamin D supplements will reduce the risk of hip fracture'. The Panel also noted that a slide set entitled 'Adoption Pathway' which instructed representatives how to sell Calcichew-D₃ Forte stated in slides 3 and 4, beneath a subheading 'Selling Action Points', 'Show evidence that calcium and vitamin D prevent hip fracture'. Slide 8 stated 'Reinforce use of Calcichew-D₃ Forte in preventing hip fracture'. Nowhere in either slide presentation was it stated that Calcichew-D₃ Forte was only licensed in osteoporosis as adjunctive therapy to specific therapy for the condition. The Panel considered that the training material implied that Calcichew-D₃ Forte was licensed in its own right for the prevention of osteoporosis. This was not so. The Panel ruled a breach of Clause 15.9 of the Code.

During its consideration of this case the Panel noted that a card supplied by Shire (ref Sept.2000 003/0110) detailed how to conduct a hip fracture risk assessment in a clinical setting. Although the card did not mention Calcichew-D₃ Forte *per se* it did refer to 'high dose calcium and vitamin D supplementation' and recommended daily doses of '500 – 1000mg calcium and 800 IU vitamin D' (equivalent to two Calcichew-D₃ Forte tablets – the licensed daily dose in adults and the elderly). No prescribing information was included on the card. The Panel considered that the card, in effect, promoted the use of Calcichew-D₃ Forte and should have included the prescribing information for the product. The Panel requested that Shire be advised of its views.

Complaint received	14 February 2001
Case completed	17 April 2001

FERRING v GLAXOSMITHKLINE

Promotion of Asacol

Ferring complained about the promotion of Asacol (mesalazine) by GlaxoSmithKline. The items at issue were a patient leaflet pad distributed to secondary care physicians and two leavpieces distributed to primary and secondary care physicians.

The strapline 'Keeping them free from IBD' appeared beneath the product logo on each item. Ferring noted that Asacol was indicated for the treatment of mild to moderate acute exacerbations of ulcerative colitis, maintenance of remission in ulcerative colitis and maintenance of remission in Crohn's ileo colitis. It was therefore not indicated for the treatment of small bowel Crohn's disease in any form. IBD was an all embracing term for inflammatory bowel disease and the use of the term was misleading in that it inferred that Asacol had a wider range of indications than it was actually licensed for. Ferring also considered that 'Keeping them free from IBD' was overstating the ability of Asacol to maintain freedom from symptoms. The company also considered this form of words to be a superlative, which could not be substantiated. The Panel noted the indications for Asacol. The term inflammatory bowel disease (IBD) was a general one that included ulcerative colitis and Crohn's disease. Although Crohn's disease most commonly occurred in the terminal ileum and the colon, any site in the gastrointestinal tract could be affected. GlaxoSmithKline had submitted that Asacol was a suitable treatment for the vast majority of patients with ulcerative colitis and Crohn's disease. The Panel considered that the claim 'Keeping them free from IBD' implied that Asacol could be used for the maintenance of remission of every patient with inflammatory bowel disease which was not so. The claim was misleading and all-embracing. Breaches of the Code were ruled. The Panel did not consider that the claim was a superlative and ruled no breach in that regard.

The claim 'A dose for dose switch between mesalazine preparations could result in lower concentrations in the terminal ileum and colon' appeared as a stabpoint beneath a heading 'The importance of branded prescribing' in one of the leavpieces. Ferring noted that this claim was referenced to a letter which had been published in *The Lancet* (Benbow and Gould 1998) which had been written in response to a previous letter concerning generic substitution of mesalazine published in the same journal (Forbes and Chadwick 1997). The letter from Benbow and Gould amounted to no more than a personal communication originating from SmithKline Beecham. Ferring noted that the reference was also misquoted and taken out of context as the original letter had stated 'A dose for dose switch from Asacol to Coltec EC may therefore result in increased release of mesalazine more proximally in the gastrointestinal tract and thus, a lower concentration in the terminal ileum and colon'. Ferring questioned the wisdom of using, as a reference, a letter prepared by SmithKline Beecham which had not been subject to peer review, but in any case, the quote could not be substantiated and was misleading. The letter was directly related to the issue of a generic competitor to Asacol that was formerly on the market and, therefore, this letter could not be used to support a promotional claim now that Coltec EC was

no longer available. The Panel noted that the claim in question did not appear as a quote; it could not therefore be considered a misquote. The letter to which the claim was referenced had detailed the mean release of mesalazine from Asacol, Coltec EC and Salofalk at pH 6.4 and shown that the release of mesalazine from Coltec EC was far greater than from the other two products. The letter also referred to a significant variation for Coltec EC between tablets (range <1% to 88%). A dose for dose switch from Asacol to Coltec EC might therefore result in an increased release of mesalazine more proximally in the gastrointestinal tract and thus a lower concentration in the terminal ileum and colon. Mesalazine from Asacol, according to the summary of product characteristics (SPC), became available when intestinal pH rose above 7, in the terminal ileum and large bowel. The Panel considered, however, that as there was no mention of any product in particular the claim in question could be read as implying that if Asacol was switched dose for dose with any other mesalazine preparation then lower doses of mesalazine would occur in the terminal ileum and the colon. This interpretation was supported by diagrams of the release profile of various mesalazine preparations. There was some data with regard to Coltec EC but not with regard to any other mesalazine preparation. The Panel considered that the claim was misleading and that it could not be substantiated. Breaches of the Code were ruled.

All of the promotional pieces showed the release characteristics of mesalazine throughout the gut from three different preparations. Ferring disputed the accuracy of the representation of the release profile of sustained release mesalazine, its product Pentasa, which suggested that the majority of the mesalazine was released high in the small bowel and that the concentration reduced significantly through the gastrointestinal tract, achieving only low levels in the distal colon. This was clearly at variance with the Pentasa SPC. The graphical representations in question were neither accurate nor balanced and Ferring also considered that they disparaged Pentasa. The Panel noted that the SPC for Pentasa stated 'Following administration and tablet disintegration the microgranules act as discrete slow-release formulations which allow a continuous release of drug from duodenum to rectum at all enteral pH conditions'. The diagram in question, however, showed that with sustained release preparations the concentration of mesalazine was uniformly high throughout the small intestine with the concentration lessening throughout the large intestine such that only low levels were achieved in the distal colon. The Panel noted GlaxoSmithKline's submission that there was no overwhelming body of evidence in favour of either

argument. The Panel noted that supplementary information to the Code on emerging clinical or scientific opinion stated that where an issue existed that had not been resolved in favour of one generally accepted viewpoint, particular care must be taken to ensure that the issue was treated in a balanced manner in promotional material. The Panel considered that the diagram was misleading with regard to the release of mesalazine from slow release formulations; it was not consistent with the information given in the Pentasa SPC. Breaches of the Code were ruled. The Panel did not, however, consider that the diagram disparaged Pentasa.

Ferring Pharmaceuticals Ltd complained about the promotion of Asacol (mesalazine) by GlaxoSmithKline. There were three promotional items at issue, a patient leaflet pad (ref AS:LP/9/025), distributed only to secondary care physicians, and two leavepieces (refs AS:LP/9/024 and AS:CC/0/001), which were distributed to primary and secondary care physicians.

1 Claim 'Keeping them free from IBD'

This strapline appeared beneath the product logo on each promotional item.

COMPLAINT

Ferring noted that Asacol was indicated for the treatment of mild to moderate acute exacerbations of ulcerative colitis, maintenance of remission in ulcerative colitis and maintenance of remission in Crohn's ileo colitis. It was therefore not indicated for the treatment of small bowel Crohn's disease in any form. IBD was an all embracing term for inflammatory bowel disease and the use of the term in the strapline was misleading in that it inferred that Asacol had a wider range of indications than it was actually licensed for. Ferring also considered that 'Keeping them free from IBD' was overstating the ability of Asacol to maintain freedom from symptoms. The company also considered this form of words to be a superlative, which could not be substantiated.

Ferring alleged that the phrase 'Keeping them free from IBD' was in breach of Clauses 7.2 and 7.8 of the Code.

RESPONSE

GlaxoSmithKline noted that it was argued that 'Keeping them free from IBD' was all-embracing in that Asacol was not indicated for the treatment of acute exacerbations of Crohn's ileo-colitis, only for the maintenance of its remission. The company considered that 'keeping them free' encapsulated this concept of maintenance in an entirely appropriate way and that a distinction should be made between 'keeps them free' and 'keeping them free' as the latter implied an on-going maintenance therapy.

GlaxoSmithKline noted that Ferring was incorrect to state that Asacol was not indicated for the treatment of small bowel Crohn's disease in any form. The ileum was part of the small bowel and the commonest site for Crohn's disease to develop followed by the

large bowel. Asacol therefore provided a suitable treatment for the vast majority of patients with ulcerative colitis and Crohn's disease and the strapline did not overstate the potential use of the product at all. The company therefore rejected the allegation of a breach of Clauses 7.2 and 7.8.

PANEL RULING

The Panel noted that Asacol was indicated for the treatment of mild to moderate acute exacerbations of ulcerative colitis and for the maintenance of remission. It was also indicated for the maintenance of remission of Crohn's ileo-colitis.

The Panel noted that the term inflammatory bowel disease (IBD) was a general one that included ulcerative colitis and Crohn's disease. Although Crohn's disease most commonly occurred in the terminal ileum and the colon any site in the gastrointestinal tract could be affected.

The Panel noted that GlaxoSmithKline had submitted that Asacol was a suitable treatment for the vast majority of patients with ulcerative colitis and Crohn's disease. The Panel considered that the claim 'Keeping them free from IBD' implied that Asacol could be used for the maintenance of remission of every patient with inflammatory bowel disease which was not so. The Panel considered that the claim was misleading and all-embracing. Breaches of Clauses 7.2 and 7.8 were ruled.

The Panel did not consider that the claim was a superlative as alleged and ruled no breach of Clause 7.8 of the Code in that regard.

2 Claim 'A dose for dose switch between mesalazine preparations could result in lower concentrations of mesalazine in the terminal ileum and colon'

This claim appeared as the second stabpoint beneath a heading 'The importance of branded prescribing' in leavepiece ref AS:LP/9/024.

COMPLAINT

Ferring noted that this claim was referenced to a letter which had been published in The Lancet (Benbow and Gould 1998) which had been written in response to a previous letter concerning generic substitution of mesalazine published in the same journal (Forbes and Chadwick 1997). The letter from Benbow and Gould amounted to no more than a personal communication originating from SmithKline Beecham. Ferring noted that the reference was also misquoted and taken out of context as the original letter had stated 'A dose for dose switch from Asacol to Coltec EC may therefore result in increased release of mesalazine more proximally in the gastrointestinal tract and thus, a lower concentration in the terminal ileum and colon'.

Ferring questioned the wisdom of using, as a reference, a letter prepared by SmithKline Beecham which had not been subject to peer review, but in any case, the quote could not be substantiated and was misleading. The letter was directly related to the

issue of a generic competitor to Asacol that was formerly on the market and therefore, this letter could not be used to support a promotional claim now that Coltec EC was no longer available.

Ferring alleged that the use of this quote was in breach of Clauses 7.2 and 7.3 of the Code.

RESPONSE

GlaxoSmithKline stated that the claim in question was not a misquote as suggested by Ferring. It was not placed between inverted commas and was not therefore a quote at all, but it did accurately reflect the opinion of the authors and was not taken out of context. The charge that this reference was inappropriate because its authors were employees of the company was not justified. The letter was a very balanced text in response to an earlier letter and was peer reviewed in that it was accepted for publication by The Lancet. The issue of the current availability of Coltec was not relevant in the context of the discussion in general and indeed the letter referred to both Coltec EC and Salofalk, which was still marketed.

GlaxoSmithKline therefore rejected the allegation of a breach of Clauses 7.2 and 7.3.

PANEL RULING

The Panel noted that the claim 'A dose for dose switch between mesalazine preparations could result in lower concentrations of mesalazine in the terminal ileum and colon' did not appear as a quote; it could not therefore be considered a misquote. The claim was referenced to a letter to The Lancet from Benbow and Gould. The letter had detailed the mean release of mesalazine from Asacol, Coltec EC and Salofalk at pH 6.4 and shown that the release of mesalazine from Coltec EC was far greater than from the other two products. The letter also referred to a significant variation for Coltec EC between tablets (range <1% to 88%). A dose for dose switch from Asacol to Coltec EC might therefore result in an increased release of mesalazine more proximally in the gastrointestinal tract and thus a lower concentration in the terminal ileum and colon. Mesalazine from Asacol, according to the summary of product characteristics (SPC), became available when intestinal pH rose above 7, in the terminal ileum and large bowel.

The Panel considered, however, that as there was no mention of any product in particular the claim in question could be read as implying that if Asacol was switched dose for dose with any other mesalazine preparation then lower doses of mesalazine would occur in the terminal ileum and the colon. This interpretation was supported by diagrams of the release profile of various mesalazine preparations. There was some data with regard to Coltec EC but not with regard to any other mesalazine preparation. The Panel considered that the claim was misleading and that it could not be substantiated. Breaches of Clauses 7.2 and 7.3 were ruled.

During its consideration of this matter the Panel noted that the fact that the authors of a reference cited in support of a medicine were employed by the

company responsible for marketing that medicine was not important, what mattered was that any reference cited was relevant. Claims had to be capable of substantiation but additional material to that cited could be supplied. References were required when promotional material referred to published studies (Clause 7.5). The Panel also noted that in its response GlaxoSmithKline had stated that the letter from Benbow and Gould was peer reviewed in that it was accepted for publication by The Lancet. The Panel noted that The Lancet currently advised that correspondence was not usually peer reviewed and questioned whether the letter from Benbow and Gould had therefore been through such a process. The Panel noted that the letter had been written in response to a previous letter published in The Lancet.

3 Pictorial representation of the release profile of mesalazine from Asacol

All of the promotional pieces showed the release characteristics of mesalazine throughout the gut from three different preparations. Azo-bonded mesalazine was shown to be released only in the large intestine with the greater concentrations occurring from the transverse colon onwards. Sustained release mesalazine was shown to produce a greater concentration throughout the small intestine with the concentration lessening in the large intestine. Asacol was shown to start releasing mesalazine in the ileum producing a uniformly greater concentration throughout the colon.

COMPLAINT

Ferring disputed the accuracy of the representation of the release profile of sustained release mesalazine ie its product Pentasa, which suggested that the majority of the mesalazine was released high in the small bowel and that the concentration reduced significantly through the gastrointestinal tract, achieving only low levels in the distal colon. The SPC for Pentasa stated that 'the microgranules act as discrete slow-release formulations which allow a continuous release of drug from duodenum to rectum at all enteral pH conditions'. The representation of the release profile for Pentasa tablets in the promotional items at issue was, therefore, clearly at variance with the Pentasa SPC in suggesting a reduction of mesalazine release through the gastrointestinal tract.

Ferring stated that with Pentasa 8.9% of the dose found in eliminated faeces remained within the microgranules, which confirmed that mesalazine continued to be available for release throughout the whole of the gastrointestinal tract (Yu *et al* 1995).

Layer *et al* (1995) had investigated the luminal concentrations of mesalazine at various sites in the small intestine to determine the human intestinal delivery pattern of Pentasa. It was shown that in the duodenum mesalazine concentrations were 52mcg/ml and acetyl mesalazine plateau concentrations were 38mcg/ml. Intrajejunal concentrations of mesalazine were 59mcg/ml and of acetyl mesalazine were 82mcg/ml; mean intraleal concentrations of

mesalazine were 64mcg/ml and of acetyl mesalazine were 104mcg/ml. The authors calculated that 82% of the dose of mesalazine from Pentasa was delivered to the colon, 75% still within the microgranules and available for release.

Christensen (2000) published a review of mesalazine products that included a section on pharmacokinetics and disposition. Data were presented on concentrations of mesalazine in ileostomy effluent and in faeces which showed that higher concentrations were consistently achieved at the rectum than in the terminal ileum and that this was dose dependent.

The graphical representations in question were, therefore, neither accurate nor balanced and Ferring stated that it also considered them to be disparaging with regard to Pentasa. The company also noted that these graphics were not referenced.

Ferring alleged that the graphical representations were in breach of Clauses 7.2 and 7.6 and 8.1 of the Code.

RESPONSE

GlaxoSmithKline stated that the matter had been the subject of much discussion between it and Ferring over a considerable period of time. Both companies could, and did, provide an abundance of evidence to support their respective positions vis-à-vis the distribution of mesalazine products within the GI tract. For example, the release pattern of sustained release mesalazine had been the subject of many studies. In two of these (Rasmussen *et al*, 1982, and Rasmussen *et al*, 1988) and quoted by Laursen *et al* (1990), only 22-45% of the ingested dose remained in the lumen after the intestinal contents had reached the colon and half was retained in the microgranules, thus suggesting a tailing off of the concentrations of the active substance as it passed through the GI tract. This is what was conveyed by the diagrammatic representation. GlaxoSmithKline accepted that all such views were simply the opinions of their respective authors. There was not, however, any overwhelming body of evidence in favour of either argument and as such the company retained the right,

as indeed did Ferring, to promote Asacol in its most favourable light. Such was the cut and thrust of marketing activity in general. No boundaries had been overstepped, Pentasa had not been disparaged and Clauses 7.2, 7.6 and 8.1 had not been breached. It was also claimed that the graphics were not referenced. References were, however, given in the text immediately above the diagrams.

PANEL RULING

The Panel noted that the SPC for Pentasa stated 'Following administration and tablet disintegration the microgranules act as discrete slow-release formulations which allow a continuous release of drug from duodenum to rectum at all enteral pH conditions'. The diagram in question, however, showed that with sustained release preparations the concentration of mesalazine was uniformly high throughout the small intestine with the concentration lessening throughout the large intestine such that only low levels were achieved in the distal colon. The Panel noted GlaxoSmithKline's submission that there was no overwhelming body of evidence in favour of either argument.

The Panel noted that the supplementary information to Clause 7.2 of the Code, emerging clinical or scientific opinion, stated that where an issue existed that had not been resolved in favour of one generally accepted viewpoint, particular care must be taken to ensure that the issue was treated in a balanced manner in promotional material. The Panel considered that the diagram was misleading with regard to the release of mesalazine from slow release formulations; it was not consistent with the information given in the Pentasa SPC. Breaches of Clauses 7.2 and 7.8 were ruled. The Panel did not, however, consider that the diagram disparaged Pentasa as alleged and ruled no breach of Clause 8.1 of the Code.

Complaint received	22 February 2001
Case completed	24 April 2001

DIRECTOR OF PHARMACEUTICAL PUBLIC HEALTH v SHIRE and JANSSEN-CILAG

Nice biscuits as promotional aid

A health authority director of pharmaceutical public health complained about a packet of Nice biscuits which he had received from Shire and Janssen-Cilag as part of the companies' co-marketing of Reminyl, a treatment for mild to moderately severe Alzheimer's dementia. A letter sent with the biscuits drew the reader's attention to the fact that the National Institute of Clinical Excellence (NICE) had recently published guidance on the therapy area. The complainant appreciated the pun but considered that the provision of biscuits was inappropriate.

The Panel noted that the cost of each packet of biscuits was within the limit of £5 excluding VAT which applied to promotional aids. The Panel did not, however, consider that the biscuits were sufficiently relevant to the practice of medicine. A breach of the Code was ruled.

A health authority director of pharmaceutical public health complained about a package he had received from Shire Pharmaceuticals Ltd and Janssen-Cilag Ltd. The companies co-marketed Reminyl (galantamine hydrobromide) which was licensed for the symptomatic treatment of mild to moderately severe Alzheimer's dementia. A letter within the package drew the reader's attention to the fact that the National Institute for Clinical Excellence (NICE) had recently published guidance on the use of therapies currently available for the treatment of mild to moderate Alzheimer's disease. Accompanying the letter was a 150g packet of Peak Freans' Nice biscuits. The letter had been widely distributed to health professionals and to health authority chief executives and directors of public health.

The complainant had written a letter of complaint to Shire and had sent a copy of it, with a covering letter, to the Authority.

COMPLAINT

The complainant, whilst appreciating the pun, considered that the provision of the biscuits was inappropriate and in breach of Clause 18.2 of the Code.

RESPONSE

Shire responded on behalf of both companies and stated that it disagreed that the provision of the Nice biscuits was in breach of Clause 18.2 of the Code because:

- The packet of Nice biscuits in question cost less than 50 pence and therefore was inexpensive as defined in the supplementary information to Clause 18.2 of the Code.

- The packet of biscuits did not carry the Reminyl, Shire or Janssen-Cilag branded logo.
- The complainant stated that he appreciated the pun.
- The relevance to the practice of medicine of this promotional aid was to draw the attention of the recipients to the NICE guidance issued on acetylcholinesterase inhibitors. There was evidence that the NHS and clinicians had reacted patchily to date to NICE guidances on pharmaceuticals. This was a light-hearted but nonetheless serious attempt to draw health professionals' interest to this important NICE guidance, to have them consider it and hopefully have them put it into practice – so that many patients and their carers could obtain some relief from the distressing condition of Alzheimer's disease.

Shire stated that it had considered the letter and gift of the Nice biscuits very carefully, believing that recipients would take them in the spirit that was intended and would as a consequence pay more attention to the NICE guidance. The company was sorry that the complainant considered that the gift of biscuits was inappropriate and unprofessional. Shire did not agree and submitted that it had complied with Clause 18.2 of the Code.

PANEL RULING

The Panel noted that Clause 18.2 required gifts in the form of promotional aids to health professionals to be inexpensive and relevant to the practice of their profession or employment. The Panel noted that Shire had confirmed that the cost to the company of each packet of biscuits was less than 50 pence. The cost came within the limit of £5 excluding VAT which applied to promotional aids.

On balance the Panel did not however consider that the packet of biscuits was sufficiently relevant to the practice of medicine. The Panel ruled that the item, by not meeting the provisions of Clause 18.2, was in breach of Clause 18.1 of the Code.

Complaint received 27 February 2001

Case completed 11 April 2001

NORTON HEALTHCARE v 3M HEALTH CARE

Qvar and Airomir 'Dear Doctor' letters

Norton Healthcare alleged that the claim 'A change for the better', in a Qvar (CFC-free beclomethasone (BDP)) 'Dear Doctor' letter, was a hanging comparison and that even if the comparator was accepted to be CFC-BDP then the claim could not be substantiated.

The Panel did not consider that the claim was a hanging comparison; it was clear that the comparator was CFC-BDP. No breach of the Code was ruled. The Panel noted that although the claim was made on the basis of effectiveness, convenience and cost, Qvar was not suitable for all patients. The Panel considered that the claim was broad and could not be substantiated; a breach of the Code was ruled.

Norton Healthcare alleged that the letter encouraged a switch from CFC-BDP to Qvar; the letter did not state that Qvar was not indicated in certain patient groups.

The Panel noted that symptomatic patients requiring more than 800mcg/day and children aged less than 12 were not suitable for treatment with Qvar. By not mentioning this the letter gave the impression that all patients on CFC-BDP could be switched to Qvar which was not so. The Panel considered that the letter was thus misleading and inconsistent with the marketing authorization. Breaches of the Code were ruled.

Norton Healthcare alleged that references in the letter, and in a letter relating to Airomir (CFC-free salbutamol), to the discontinuation of a leading manufacturer's breath actuated metered dose inhaler were misleading and ambiguous. The position was in fact that the leading manufacturer was transferring the marketing of the metered dose inhalers to Baker Norton and that this change in responsibility would result in simple livery transitions/product name changes. Norton Healthcare alleged that the intentional confusion with regard to the availability of competitor products reflected poorly on the industry in breach of Clause 2 of the Code.

The Panel noted that a similar matter had been considered in Case AUTH/1136/2/01. Letters in that case had referred to the discontinuation of certain inhalers but the Panel considered that this was too simplistic; the products still existed but had been given new brand names. A breach of the Code was ruled which had been accepted by 3M Health Care. The Panel considered that the allegations in this case were covered by its ruling in the previous case. This case, however, also included allegations of a breach of Clause 2 of the Code, a sign of particular censure. On balance the Panel did not consider that the circumstance warranted such a ruling and no breach of Clause 2 was ruled.

Norton Healthcare Limited complained about two 'Dear Doctor' letters sent by 3M Health Care Limited. One (ref 1200/QV/004/045) related to Qvar (CFC-free beclomethasone dipropionate (BDP)) and the other (ref 1200/A1/002/01) related to Airomir (CFC-free salbutamol sulphate).

A Qvar mailing

1 Claim 'A change for the better'

COMPLAINT

Norton Healthcare alleged a breach of Clause 7.2 of the Code because of the use of a hanging comparator 'A change for the better'. The mailing failed to make clear or adequately substantiate which medicine(s) was/were the subject of the comparison. Even in the event that one accepted that the comparator was indeed 'CFC-BDP', then Norton Healthcare argued strongly that the claim of 'A change for the better' was not substantiated by two 3M Health Care sponsored publications one of which, Davies *et al*, was a non-peer reviewed journal supplement. This clearly fell short of the criteria most would apply in determining consensus as to the balance of scientific opinion on a given issue. In this regard a breach of Clause 7.3 was also alleged.

RESPONSE

3M Health Care stated that Norton Healthcare complained that the strapline failed to make clear the medicine that was the subject of the comparison. In the mailing, the header strapline was followed by claims for Qvar on deposition, clinical effect and cost compared to CFC-beclomethasone (CFC-BDP). The claim was substantiated by references. Clause 7.2 provided guidance on the use of hanging comparisons. In this instance the medicine with which the comparison was made, namely CFC-BDP, was clearly stated and was therefore not a breach of the Code.

Norton Healthcare went on to accept that the comparator was clear but complained that the claim was not substantiated by references. The claims against CFC-BDP included greater lung deposition and effectiveness at half the dose of conventional CFC-BDP.

The deposition data for Qvar when compared to CFC BDP had already been the subject of a complaint by Glaxo Wellcome when no breach of the Code was found (Case AUTH/789/11/98). A more recent ruling also found no breach of the Code for the same claim (Case AUTH/1110/12/00) in response to a complaint by Glaxo Wellcome.

With regard to the claim that Qvar was effective at half the dose of conventional CFC-BDP, the references provided clearly substantiated the claim. The Gross *et al* study was conducted on 347 patients with symptomatic asthma. After establishing control the patients were randomised to treatment with HFA-BDP (Qvar) 400 mcg/day, CFC-BDP 800 mcg/day or HFA-placebo for a 12-week period. The results showed and the paper concluded that HFA-BDP (Qvar) provided equivalent control of moderate or moderately severe asthma as CFC-BDP in the population studied, but at half the total daily dose.

The Davies *et al* study was similar in design and

conducted in 233 patients with moderately severe, symptomatic asthma. It concluded that HFA-BDP extrafine aerosol was found to provide equivalent control of moderately severe asthma to CFC-BDP at approximately half the daily dose, with a favourable safety profile, suggesting an improved therapeutic ratio.

3M Health Care submitted that both the studies therefore substantiated the claim of Qvar being effective at half the dose of conventional CFC-BDP and were not misleading or in breach of the Code.

The claim 'A change for the better' was made for Qvar on the grounds of equivalent effectiveness at half the daily dose of CFC-BDP and the time saved on future changes to CFC-free inhalers as these patients were already undergoing a change to their prescription. It was also made on the grounds of a cost saving from Allen and Hanburys' discontinued CFC-BDP breath actuated inhaler to Qvar Autohaler. This claim was also referenced. A change to Qvar Autohaler as per the summary of product characteristics (SPC) in these patients would therefore be associated with a cost saving from their previous CFC-BDP prescription and provided equivalent effectiveness of asthma control. It might also save time in the future should these patients be transferred to CFC-free inhaled steroid treatment. 3M Health Care therefore contended that the claim was valid and was supported by appropriate references. 3M Health Care denied a breach of Clause 7.3 of the Code.

PANEL RULING

The Panel noted that the letter was headed 'A change for the better' which was followed by 'You may not be aware of the recent discontinuation of a leading manufacturer's breath-actuated beclomethasone dipropionate (CFC-BDP) metered dose inhaler'. The letter explained that patients using this brand would have to change at their next prescription and in future they might also have to change again to a CFC-free breath-actuated inhaler unless they were switched to Qvar.

The Panel considered that the claim 'A change for the better' was not a hanging comparison as alleged. It was clear that the comparison was between CFC-BDP and Qvar. No breach of Clause 7.2 of the Code was ruled in that regard.

With regard to the data provided by 3M to substantiate the claim, the Panel noted that it was not necessarily a breach of the Code to use company sponsored material to support promotional material. The question for the Panel was whether the data supplied substantiated the claim.

The Panel noted the submission from 3M Health Care that the claim was made on the grounds of equivalent effectiveness at half the daily dose of CFC-BDP, the time saved on future changes to CFC-free inhalers and the cost saving compared with Allen and Hanburys' discontinued CFC-BDP. Qvar was not suitable for all patients as referred to in A2 below. The Panel considered that the claim 'A change for the better' was a broad claim which could not be substantiated. A breach of Clause 7.3 of the Code was ruled.

2 Unauthorized indications

COMPLAINT

Norton Healthcare alleged that the mailing was in essence an encouragement to switch patients from CFC-BDP to Qvar Autohaler. No mention was made as to the fact that Qvar was not indicated in certain patient groups and specifically in children under 12 years of age.

RESPONSE

3M Health Care stated that the SPC provided guidance on transferring patients with poorly controlled asthma from a CFC-containing inhaler and recommended that initially a 100mcg metered dose of Qvar should be substituted for a 100mcg of beclomethasone dipropionate or budesonide.

The prescribing information on Qvar provided with the item clearly specified that the maximum recommended dose was 800mcg per day and that there were no definitive dosage data for children under 12 years age. 3M Health Care contended that a qualified practitioner would not reasonably misinterpret the claim and would also be expected to refer to the prescribing information or the SPC if he/she were unfamiliar with the use of Qvar.

3M Health Care did not agree that the claim encouraged use outside the terms of the marketing authorization or that it breached Clause 3.2 of the Code and added that it would never encourage the use of any product outside of its marketing authorization.

The alleged breach of Clause 3.2 of the Code was similar to that at issue at point A4 in Case AUTH/1110/12/00 that was the subject of a recent appeal by 3M Health Care. 3M Health Care stated that it had responded to the allegation in accordance with the advice provided by the Authority.

PANEL RULING

The Panel noted that there were patient groups for whom Qvar was not suitable such as symptomatic patients requiring more than 800mcg/day and children under 12 years. By making no mention of these exceptions the letter gave the impression that all patients on CFC-BDP could be simply transferred to Qvar and that was not so. The Panel considered that the letter was misleading in this regard and was inconsistent with the marketing authorization. A breach of Clause 3.2 was ruled.

The Panel noted that a similar case had been considered by the Appeal Board in relation to different material.

3 Reference to discontinuation of breath-actuated BDP

COMPLAINT

Norton Healthcare stated that the mailing opened with a reference to the recent discontinuation of a leading manufacturer's breath-actuated beclomethasone dipropionate (CFC-BDP) metered dose inhaler. Whilst 3M Health Care's subsequent

correspondence acknowledged the products in question to be Becotide 50 and Becotide 100 Easi-Breathe and Becloforte Easi-Breathe, its defence of the statement Norton Healthcare found wholly unsatisfactory. Indeed, by way of defence, 3M Health Care cited Baker Norton's own previous mailing to healthcare professionals headed 'Easi-Breathe name changes in the UK'. Thus the position in the marketplace was well known, namely that GlaxoWellcome and Baker Norton were co-operating in a simple livery transition/product name change. Norton Healthcare continued to assert that this did not constitute a discontinuation in the manner implied by 3M Health Care and that this would not be the interpretation of a reasonable healthcare professional. Norton Healthcare was bound to raise the question as to 3M Health Care's intent in presenting such change in a disingenuous and mischievous manner. In many years of experience Norton Healthcare could not recall a similar situation where availability of a competitor product to the healthcare community was so intentionally confused. This reflected poorly on the industry image and had impact beyond the simply mischievous and irresponsible. A breach of Clause 2 was alleged. Norton Healthcare further alleged a breach Clause 7.2 of the Code in that the mailing was clearly misleading and ambiguous.

RESPONSE

3M Health Care stated that it noted that the complaint referred specifically to the use of the phrase 'recent discontinuation' and stated that 3M Health Care was disingenuous in claiming that a leading manufacturer's breath actuated beclomethasone dipropionate (CFC-BDP) metered dose inhaler was discontinued. Norton Healthcare correctly identified the products referred to as Allen and Hanburys' brands of CFC-BDP Easi-Breathe, namely Becloforte and Becotide Easi-Breathe. 3M Health Care did not use the brand name in the promotional item in keeping with Clause 7.10 of the Code.

3M Health Care's understanding was that branded Becotide and Becloforte Easi-Breathe products manufactured by Allen and Hanburys were no longer available. Baker Norton had resumed responsibility for marketing Easi-Breathe in the UK in that it had taken over the responsibility for the sales and marketing of the inhalation device Easi-Breathe. The device was being used to deliver Beclazone. The branded medicines, Becloforte and Becotide, were still a trade mark of Allen and Hanburys, to 3M Health Care's knowledge. These Allen and Hanburys branded breath-actuated products were effectively discontinued.

3M Health Care provided an article from Chemist and Druggist, 17 February 2001. The article, which appeared to be a press release by Norton Healthcare, clearly stated in the second paragraph that the breath-actuated salbutamol pMDI from a different manufacturer had been discontinued. 3M Health Care was then surprised that Norton Healthcare complained of the use of the term 'discontinued' by 3M Health Care.

A mailing on the subject by Baker Norton which was provided clearly specified that the Allen and

Hanburys Easi-Breathe brands and the Baker Norton Easi-Breathe brands were not interchangeable by pharmacists or dispensers when filling a prescription. It provided important information about Easi-Breathe and clearly implied, as had been highlighted in the letter in question, that the patient prescription would be changed as a result.

The letter in question stated 'that patients currently taking the brand of a leading manufacturer's breath-actuated beclomethasone dipropionate MDI may need to change at the next prescription.' This information was accurate and did not mislead the health professional. Patients who were on Becotide and Becloforte Easi-Breathe would no longer be able to receive the branded product and prescribers would be unable to prescribe Becotide and Becloforte Easi-Breathe by brand. 3M Health Care was all too aware of patients' concerns when they were switched to different medicinal products without due consideration. In this case pharmacists would be required to explain the change to patients. 3M Health Care therefore contended that the branded drug-device combination of Allen and Hanburys' Easi-Breathe products were discontinued and that the phrase 'recent discontinuation' was not misleading and not in breach of Clause 2 or Clause 7.2 of the Code.

The letter from 3M Health Care highlighted that patients' inhaler medication would need to be changed in view of the discontinuation of Ventolin, Becloforte and Becotide Easi-Breathe products and promoted the 3M respiratory brands as credible, cost-efficient, alternative breath-actuated products. The letter from Norton Healthcare highlighting the change in patients' inhalational treatment was, in principle, equally informative for its products, as were the letters from 3M Health Care and in the latter's opinion, were not attempts at market manipulation or deception.

3M Health Care wished to state that it was never its intention to mislead healthcare professionals and it endeavoured to work within the Code when dealing with members of the health profession.

PANEL RULING

Firstly the Panel noted that there had been a similar complaint regarding a Qvar letter and an Airomir letter, Case AUTH/1136/2/01. In that case the Panel had noted the submission from 3M Health Care that it could not refer by brand name to the products which had been withdrawn as brand names of other companies' products could not be used unless prior consent had been obtained (Clause 7.10 of the Code). This had complicated matters. The Panel had examined the 'Dear Healthcare Professional' letter produced by Baker Norton about the matter and provided by 3M Health Care. The letter was headed 'Easi-Breathe name changes in the UK' and had stated that Baker Norton would be resuming responsibility for marketing Easi-Breathe in the UK, listed the changes to the Easi-Breathe brand names and stated that, *inter alia*, the dose, strength and pack size would remain the same. The Ventolin Easi-Breathe brand and the Becotide Easi-Breathe brand range had been discontinued.

The Panel had noted that the medicines and device remained available as Salamol Easi-Breathe and Beclazone Easi-Breathe from Baker Norton. The products according to the complainant were unchanged and had not been discontinued; they had solely changed their brand names.

The Panel had considered that the letters at issue failed to reflect the situation. It was too simplistic to state that the products had been discontinued, the products still existed but had been given new brand names. The position had not been made sufficiently clear. Each letter was ruled in breach of Clause 7.2 of the Code. 3M Health Care had recently provided the undertaking in that case.

Turning to the case before it, Case AUTH/1148/2/01, in relation to the Qvar mailing, the Panel ruled that the alleged breach of Clause 7.2 had been covered by the Panel's ruling in the previous case. The previous case concerned a letter of similar content. The only material difference being to whom it was addressed. This ruling had been accepted by 3M Health Care.

The Panel noted that the case now before it included an allegation of a breach of Clause 2 of the Code. The Panel noted that Clause 2 of the Code was used as a sign of particular censure and reserved for such circumstances. On balance the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 and no breach of that clause was ruled.

B Airomir mailing

1 Reference to discontinuation of breath-actuated pMDI

COMPLAINT

Norton Healthcare said that the substance of its complaint about the Airomir mailing mirrored that above in point A3 with regard to the reference to 'the recent discontinuation of a leading manufacturer's breath-actuated pMDI' and a breach of Clause 2 was alleged. A breach of Clause 7.2 was also alleged as the interpretation of the Easi-Breathe name change as a 'discontinuation' was clearly misleading and ambiguous.

RESPONSE

3M Health Care stated that it noted that the complaint referred specifically to the use of the phrase 'recent discontinuation' and stated that 3M Health Care was inaccurate in claiming that a leading manufacturer's breath actuated salbutamol pMDI was discontinued. The complainant had correctly identified that the product referred to was Allen and Hanburys' brand of Ventolin, Easi-Breathe. 3M Health Care did not use the brand name in the promotional item in keeping with Clause 7.10 of the Code.

It was 3M Health Care's understanding that branded Ventolin Easi-Breathe distributed and branded by Allen and Hanburys was no longer available. Baker Norton had resumed responsibility for marketing Easi-Breathe in the UK in that it had taken over the responsibility for the sales and marketing of the

inhalational device, Easi-Breathe. The device was being used to deliver the drug, Salamol. The branded medicine, Ventolin, was still a trade mark of Allen and Hanburys, to 3M Health Care's knowledge. This Allen and Hanburys' branded breath-actuated Ventolin Easibreathe product was discontinued. An article from Chemist and Druggist, which appeared to be a press release by Norton Healthcare, clearly stated in the second paragraph that the breath-actuated salbutamol pMDI from a different manufacturer had been discontinued. 3M Health Care was then surprised that Norton Healthcare complained of the use of the term 'discontinued' by 3M Health Care.

A mailing on this subject by Baker Norton which was provided, clearly specified that the brands were not interchangeable by pharmacists or dispensers when filling a prescription. It provided important information about Easi-Breathe and clearly implied, as had been highlighted in the letter in question, that the patient prescription would be changed as a result.

The letter from 3M Health Care stated, 'that patients who are currently taking this brand of a leading manufacturer's breath-actuated salbutamol pMDI may need to change at the next prescription.' This information was accurate and did not mislead the health professional. Patients who were on Ventolin Easi-Breathe would no longer be able to receive the branded product and prescribers would be unable to prescribe Ventolin Easi-Breathe by brand. 3M Health Care was all too aware of patients' concerns when they were switched to different medicinal products without due consideration. In this case pharmacists would be required to explain the change to patients. 3M Health Care therefore contended that the branded drug-device combination was effectively discontinued and that the phrase 'recent discontinuation' was not misleading and not in breach of Clause 2 or Clause 7.2 of the Code.

PANEL RULING

The Panel noted its comments in A3 above about the previous case, Case AUTH/1136/2/01, which concerned an Airomir letter that had been ruled in breach of Clause 7.2 of the Code.

Turning to the case now before it, Case AUTH/1148/2/01, the Panel ruled that the alleged breach of Clause 7.2 with regard to the Airomir mailing had been covered by its ruling in the previous case which concerned a letter of similar content. The differences being the letter presently the subject of complaint was headed 'The right choice?' and addressed to doctors, the previous case concerned a letter headed 'The right recommendation' and was addressed 'Dear Colleague'. The ruling had been accepted by 3M Health Care.

As in point A3 above a breach of Clause 2 was also alleged. The Panel decided that its ruling of no breach of Clause 2 in point A3 would also apply to the Airomir letter.

Complaint received **26 February 2001**

Case completed **20 April 2001**

SERONO v DENFLEET

Alleged promotion of unlicensed medicine

Serono stated that it had been brought to its attention that Denflect had been providing copies of the summary of product characteristics (SPC) for its product Merional (Menotrophin Injection BP) to clinicians. Serono understood that Merional had not been granted a marketing authorization and a breach of the Code was alleged. Furthermore, the SPC was misleading in that marketing authorization numbers were provided. A letter provided by Serono was from a manager at Denflect and said that the writer had promised to send information about Merional which had been requested. It pointed out that the product was not yet licensed and that a draft SPC was enclosed.

The Panel noted that it was difficult in this case to determine exactly what had happened. The complaint concerned an exchange between Denflect's manager and a hospital doctor; the complainant was not the hospital doctor and the manager had since left Denflect. The letter implied that both had recently been at the same meeting. It appeared to be a response to a genuine request from the hospital doctor for information about Merional. The letter stated that the product was yet to be licensed but it was available on a named patient basis. The cost of the product was stated in the letter and a copy of the draft SPC was enclosed. Serono had alleged that an example of a letter that the doctor might use if he was to request Merional on a named patient basis was also enclosed, although this was denied by Denflect.

The Code stated that the term 'promotion' did not include, *inter alia*, replies made in response to individual enquiries from members of the health professions, but only if they related solely to the subject matter of the enquiry, were accurate, did not mislead and were not promotional in nature. The Panel considered that, on the basis of the information before it, the letter had been written and supplied with the draft SPC in response to a genuine enquiry. Although the product was not licensed it was not unreasonable to provide a draft SPC to a doctor who might consider prescribing it on a named patient basis. In other circumstances it was unacceptable to provide a draft SPC. The inclusion of marketing authorization numbers on a draft SPC might give the impression that the product had a marketing authorization and it would be more appropriate not to include the numbers. In this particular case the draft SPC was so headed and the letter made reference to the draft SPC. The use of the example letter as an attachment was disputed by Denflect. The Code did not prohibit the supply of medicines on a named patient basis. The Panel did not consider that Denflect had promoted Merional prior to the grant of its marketing authorization and no breach of the Code was ruled.

COMPLAINT

Serono Pharmaceuticals Ltd stated that it had been brought to its attention that Denflect International Limited had been providing copies of the summary of product characteristics (SPC) for its product Merional (Menotrophin Injection BP) to clinicians. Copies of the SPC and a letter sent by Denflect were provided.

Serono understood that Merional had not been granted a marketing authorization by the Medicines Control Agency (MCA) and alleged that Denflect was in breach of Clause 3.1 of the Code which required that 'A medicine must not be promoted prior to the grant of the marketing authorization which permits its sale or supply.' Furthermore, the SPC was misleading in that marketing authorization numbers were provided under Section 8. This was incorrect as the marketing authorization had not been granted.

The letter provided by Serono was from a manager at Denflect Pharmaceuticals Ltd to an undisclosed addressee and said that the writer had promised to send information about Merional which had been requested. It pointed out that the product was not yet licensed and that a draft SPC was enclosed. This bore marketing authorization numbers. Also enclosed with the letter was an example of a letter which could be used to request Merional on a named patient basis.

RESPONSE

Denflect Pharmaceuticals Ltd stated that Denflect prescription medicines were its responsibility as part of the Denflect group. The company stated:

- 1 A product licence application for Merional was currently being evaluated by the MCA. Denflect did not possess a marketing authorization for this product.
- 2 Denflect denied that it had promoted an unlicensed product. Any information that had been supplied to a member of the medical profession had been given in response to a specific request for information.
- 3 The letter in question was addressed to a consultant obstetrician and gynaecologist in October. It was sent by an employee who tendered his resignation just prior to Denflect receiving this complaint. Denflect had no idea that this letter had been written or sent until the complaint was received. The letter had been written on the employee's personal home computer and had not gone through any head office approval system.
- 4 Denflect had undertaken as much investigation into this matter as the current situation afforded it. The letter to the consultant was in response to a specific request for the information.
- 5 The draft SPC, taken from the product licence application, was marked up as 'DRAFT' and was provided in response to a request for technical information. The accompanying letter clearly stated that the SPC was a draft.
- 6 Denflect was most concerned at the alleged inclusion of the example letter. The employee denied that this document was included in the enclosures with the letter. However, the presence of it in the complaint was most worrying. The use of such a

letter would never be condoned by Denflect; indeed, it would always be expressly forbidden. Were it to be demonstrated that the letter did emanate from Denflect, then it would most certainly be viewed as a maverick activity punishable by disciplinary action.

7 Denflect took its responsibilities seriously regarding the regulations governing the pharmaceutical industry. The need for compliance with the Code had been emphasised to this particular employee. Denflect was even more surprised since this particular individual had had many years' experience in both sales and product development, having previously worked for the complainant for many years. Such a lapse in procedure or discipline as appeared to have happened in this particular case was most unexpected. Denflect also found it hard to explain why it occurred or why the complainant received the information in such a timely fashion, immediately following the resignation of the individual concerned.

8 For obvious reasons, Denflect was endeavouring to ascertain if there were any similar letters that had been sent by this particular individual, again without its knowledge or approval.

9 Denflect had instituted the following changes as a consequence of this complaint

- a company employees would retain no headed notepaper outside the office;
- b all letters referring to products would be signed-off by a designated member of the company;
- c information of a technical nature relating to an unlicensed product would be entitled 'Technical Information', contain no reference to marketing authorization numbers and would only be provided in response to requests in writing;
- d the draft SPC would not be made available;
- e future employees would be given formal appropriate training on the Code.

A company must take responsibility for the actions of its employees and could put in place control systems to prevent abuse. These procedures would usually have a final recourse of a disciplinary nature. There was little direct action left open to Denflect in this particular case as the employee had already left employment to join a competitor and the company could have little impact on his future behaviour.

PANEL RULING

The Panel noted that it was difficult in this case to determine exactly what had happened. The complaint concerned an exchange between the Denflect manager and a hospital doctor; the complainant was not the hospital doctor and the

manager had since left Denflect's employ.

The Panel noted that the letter from the manager to the hospital doctor implied that both had recently been at the same meeting. The letter appeared to be a response to a genuine request from the hospital doctor for information about Merional. The letter stated that the product was yet to be licensed but that in the meantime it was available on a named patient basis. The cost of the product was stated in the letter and a copy of the draft SPC was enclosed. Serono also alleged that a copy of an example of a letter that the doctor might use if he was to write to Denflect requesting Merional on a named patient basis was also enclosed, although this was denied by Denflect.

The Panel noted that Clause 1.2 of the Code stated that the term 'promotion' did not include, *inter alia*, replies made in response to individual enquiries from members of the health professions, but only if they related solely to the subject matter of the enquiry, were accurate, did not mislead and were not promotional in nature.

The Panel considered that, on the basis of the information before it, the letter had been written and supplied with the draft SPC in response to a genuine enquiry. Although the product was not licensed it was not unreasonable to provide a draft SPC to a doctor who might consider prescribing it on a named patient basis. In other circumstances it was unacceptable to provide a draft SPC. The supplementary information to Clause 3.1 Advance Notification of New Products or Product Changes stated that a draft SPC, *inter alia*, should not be provided with such information. The Panel considered that the inclusion of marketing authorization numbers on a draft SPC might give the impression that the product had a marketing authorization. It would be more appropriate not to include the numbers. In this particular case the draft SPC was so headed and the letter made reference to the attached draft SPC. The use of the example letter as an attachment was disputed by Denflect. The Code did not prohibit the supply of medicines on a named patient basis. Nonetheless, the Panel was concerned regarding the circumstances in which the letter was written and noted that, following receipt of the complaint, Denflect had instituted changes to ensure that such circumstances did not recur.

The Panel did not consider that Denflect had promoted Merional prior to the grant of its marketing authorization. No breach of Clause 3.1 was ruled.

Complaint received **6 March 2001**

Case completed **25 April 2001**

CODE OF PRACTICE REVIEW – MAY 2001

Cases in which a breach of the Code was ruled are indexed in **bold type**.

1090/10/00	Anonymous v Pharmax	Promotion of Syscor MR	Breaches Clauses 2, 9.1 and 18.1	Appeal by respondent	Page 4
1096/11/00	AstraZeneca v Allen & Hanburys	'Dear Doctor' letter about Accuhaler	Five breaches Clause 7.2	Appeal by respondent	Page 9
1100/11/00	Abbott v Roche	Promotion of Fortovase and Viracept and conduct of representatives	Five breaches Clause 3.2 Breaches Clauses 4.1, 8.1 and 20.2 Three breaches Clause 10.1 Two breaches Clause 15.2	Appeal by respondent	Page 22
1103/11/00	Hospital Pharmacist v Schering-Plough	Clarityn and Nasonex promotional item	No breach	No appeal	Page 37
1105/11/00	Sanofi-Synthélabo v UCB Pharma	Promotion of Keppra	Breaches Clauses 4.1, 6.1 and 7.2	Appeal by respondent	Page 39
1106/11/00	Pharmacia v Galen	Promotion of Regurin	No breach	Appeal by respondent	Page 42
1108/11/00	Aventis Pasteur MSD v SmithKline Beecham	Engerix B promotional poster	Two breaches Clause 7.2	No appeal	Page 44
1109/11/00	Pharmacy Manager v Pfizer	Outcomes guarantee in a study	No breach	No appeal	Page 48
1110/12/00	Glaxo Wellcome v 3M Health Care	Promotion of Qvar and Airomir	Breaches Clauses 3.2, 4.6 and 7.8 Four breaches Clause 7.2 Two breaches Clause 10.1	Appeal by respondent	Page 51
1114/1/01 & 1116/1/01 to 1120/1/01	Pharmaceutical/Prescribing Advisers and Prescribing Lead v Janssen-Cilag and Organon Laboratories	Risperdal letter and tablet recognition leavpiece	Breaches Clauses 3.2 and 7.2	No appeal	Page 69
1115/1/01	GlaxoSmithKline v Lundbeck	Cipramil detail aid	Two breaches Clause 3.2 Breach Clause 4.1 Four breaches Clause 7.2	No appeal	Page 74
1122/1/01	Consultant Surgeon v Merck Sharp & Dohme	Fosamax 'Dear Doctor' letter	Breach Clause 4.1	No appeal	Page 80
1124/1/01 & 1125/1/01	Sanofi-Synthélabo v Yamanouchi Pharma and GlaxoSmithKline	Flomax MR journal advertisement	No breach	No appeal	Page 81
1126/1/01	Bioglan Laboratories v Yamanouchi Pharma	Zineryt journal advertisement	Two breaches Clause 7.2	No appeal	Page 84
1127/1/01	Health Authority Prescribing Manager v Merck Pharmaceuticals	Alcoholism awareness campaign	No breach	No appeal	Page 88
1128/1/01 & 1129/1/01	Head of Prescribing and Medicines Management v Janssen-Cilag and Organon Laboratories	Risperdal leaflet and tablet recognition leavpiece	Breach Clause 7.2	No appeal	Page 91

1136/2/01	Primary Care Pharmacist v 3M Health Care	'Dear Pharmacist' letters about Airomir and Qvar	Two breaches Clause 7.2	No appeal	Page 95
1138/2/01	General Practitioner v Shire	Promotion of Calcichew-D ₃ Forte	Breaches Clauses 3.2, 7.2 and 15.9	No appeal	Page 97
1143/2/01	Ferring v GlaxoSmithKline	Promotion of Asacol	Three breaches Clause 7.2 Breach Clause 7.3 Two breaches Clause 7.8	No appeal	Page 101
1145/2/01 & 1146/2/01	Director of Pharmaceutical Public Health v Shire and Janssen-Cilag	Nice biscuits as promotional aid	Breach Clause 18.1	No appeal	Page 105
1148/2/01	Norton Healthcare v 3M Health Care	'Dear Doctor' letters about Airomir and Qvar	Breaches Clauses 3.2 and 7.3	No appeal	Page 106
1156/3/01	Serono v Denfleet	Alleged promotion of unlicensed medicine	No breach	No appeal	Page 110

PRESCRIPTION MEDICINES CODE OF PRACTICE AUTHORITY

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

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

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

It covers:

- journal and direct mail advertising
- the activities of representatives including detail aids and other printed material used by representatives
- the supply of samples
- the provision of inducements to prescribe, supply or buy medicines by the gift, offer or promise of any benefit or bonus, whether in money or in kind
- the provision of hospitality
- the organisation of promotional meetings
- the sponsorship of scientific and other meetings including payment of travelling and accommodation expenses in connection therewith

- the provision of information to the general public either directly or indirectly
- all other sales promotion in whatever form, such as participation in exhibitions, the use of audio-cassettes, films, records, tapes, video recordings, electronic media, interactive data systems, the Internet and the like.

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

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

Complaints about the promotion of medicines should be sent to the Director of the Prescription Medicines Code of Practice Authority, 12 Whitehall, London SW1A 2DY (telephone 020 7930 9677 facsimile 020 7930 4554).