PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

NUMBER 51 FEBRUARY 2006

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.

Complaints in 2005 down on 2004

In 2005 the Authority received 101 complaints under the Code of Practice as compared with 119 in 2004. There were 131 complaints in 2003, 127 in 2002 and 138 in 2001.

The average number of complaints received each year since the Authority was established at the beginning of 1993 is 123, the numbers in individual years ranging from 92 in 1993 to 145 in both 1994 and 1997 without any perceptible reason for the variations seen.

There were 108 cases to be considered in 2005, as compared with 119 in 2003. The number of cases usually differs from the number of complaints because some complaints involve more than one company and because some complaints do not become cases at all, usually because no *prima facie* case is established.

The number of complaints from health professionals has exceeded the number from pharmaceutical companies, there having been 52 from health professionals and 28 from pharmaceutical companies (both members and non-members of the ABPI). Complaints made by pharmaceutical companies are generally more complex than those from outside the industry, usually raising a number of issues.

One complaint was made by a member of the public, three by anonymous pharmaceutical company employees. There were six other anonymous complaints, three complaints were made by organisations.

The remaining eight complaints were nominally made by the Director, and arose from media criticism, other complaints, voluntary admissions and alleged breaches of undertaking.

New Appeal Board Chairman

Mr William Harbage QC has been appointed Chairman of the Code of Practice Appeal Board and is welcomed by the Authority. Mr Harbage succeeds Mr Nicholas Browne QC who is now a Crown Court Judge.

Since taking silk in 2003, Mr Harbage has specialised in the criminal field, his cases involving murder, manslaughter, serious sexual offences, drug trafficking and misconduct in public office.

Mr Harbage has been a Recorder on the Midland Circuit since 1999. He sits in a judicial capacity for about five weeks each year trying both criminal and civil cases.

Chairman of Appeal Board appointed Crown Court Judge

The Chairman of the Code of Practice Appeal Board, Mr Nicholas Browne QC, has been appointed a Crown Court Judge.

The Authority congratulates Mr Browne on this prestigious appointment but will be sorry to lose him as Chairman of the Appeal Board.

Serono Corrective Statement

Serono Pharmaceuticals Ltd has been required to issue a corrective statement by the ABPI Board of Management following breaches of the Code. Full details can be found at page 26 of this issue of the Review in the report for Case AUTH/1708/5/05.

Public reprimand for GlaxoSmithKline

GlaxoSmithKline UK Limited has been publicly reprimanded by the ABPI Board of Management for a breach of undertaking. The ABPI Board considered this to be an extremely serious matter. Compliance with undertakings was important for effective self regulation.

Full details can be found at page 15 of this issue of the Review in the report for Case AUTH/1689/3/05.

Suspension of Abbott from ABPI

Abbott Laboratories Limited has been suspended from membership of the ABPI for a minimum of six months by the ABPI Board of Management following breaches of the Code. The ABPI Board noted that this was one of the most serious cases it had considered. It appreciated that the current management was taking action to avoid recurrence in the future. The suspension took effect from 1 January 2006 with the minimum six month period ending on 30 June 2006. Abbott Laboratories Limited will be required to comply with the Code during the period of suspension.

Full details can be found at page 74 of this issue of the Review in the report for Case AUTH/1745/7/05.

Make it formal

Companies are requested to remind all employees that when they plan a meeting for health professionals and appropriate administrative staff at outside venues, hospitality must be secondary to the purpose of the meeting. To ensure that the meeting has a clear educational content organisers would be well advised to draw up, in advance, a formal agenda detailing the subjects to be discussed, together with timings where appropriate, and issue that as part of the invitation to the meeting.

Invitations should be carefully worded so that delegates are attracted by the programme and not the associated hospitality or venue. The venue should be suitable for the purpose; the Code of Practice Panel is likely to rule any educational meeting held in an area of a restaurant, which at the same time is open to members of the public, in breach of the Code. A useful criterion in determining whether the arrangements for any meeting are acceptable is to ask 'Would I and my company be willing to have these arrangements generally known?'. The impression that is created by the arrangements for any meeting can be as important in determining its acceptability under the Code as the arrangements themselves. Companies are reminded that they risk being ruled in breach of Clause 2 of the Code in relation to meetings where the hospitality is out of proportion to the occasion and/or the educational content is slim.

Use of third parties to organize meetings

The Code of Practice Panel has considered a small number of cases where representatives have delegated some of the responsibility for organizing a meeting to a third party. Companies should remind representatives that in such circumstances the representative nonetheless remains responsible for all aspects of the meeting and the company remains liable for it under the Code. It is beholden upon representatives to ensure that any third party to whom they entrust any aspect of organization of a meeting is fully conversant with the relevant requirements of the Code. Such requirements extend beyond Clause 19, for example posters advertising a meeting must not unwittingly be turned into promotional material by someone unfamiliar with the Code. The first priority of a representative in organizing a meeting is to ensure it complies with the Code regardless of the offers of help or arrangements made by others. Responsibility for compliance cannot be delegated to third parties.

CODE OF PRACTICE TRAINING

Training seminars on the Code of Practice, run by the Prescription Medicines Code of Practice Authority and open to all comers, are held on a regular basis in central London.

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

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

Friday, 10 March

Friday, 9 June

Monday, 10 July

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 4).

How to contact the Authority

Our address is:

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12 Whitehall
London SW1A 2DY

www.pmcpa.org.uk

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 5).

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.

CASE AUTH/1652/11/04

PARAGRAPH 17/DIRECTOR v WYETH

Switch programme

During its consideration of a previous case, Case AUTH/1606/7/04, about a switch programme run by Wyeth Pharmaceuticals which would assist doctors to, *inter alia*, switch patients from Zoton to Zoton FasTab, the Panel decided that certain matters, not the subject of the complaint, be taken up with Wyeth in accordance with Paragraph 17 of the Constitution and Procedure.

During its consideration of Case AUTH/1606/7/04 the Panel was concerned about the arrangements for the implementation of the revised service. The Panel queried whether the role of the representative in the provision of the service met the requirements of the Code. The representative promoted Zoton FasTab and the service was introduced, according to the Flow chart, after the representative had promoted a switch from lansoprazole capsules to Zoton FasTab. The Panel was concerned that the role of the representative in relation to the service was linked to the promotion of Zoton FasTab and this would be the impression given to GPs. The Panel thus decided to take up its concerns as a separate complaint with Wyeth (Case AUTH/1652/11/04). This was in accordance with Paragraph 17.1 of the Constitution and Procedure.

In considering the present case, Case AUTH/1652/11/04 the Panel noted that Wyeth maintained that its representatives could introduce the service in a clearly distinct and separate part of the same GP call as the promotion of Zoton FasTab provided no product promotion took place during the GastroCare service discussion.

The Panel noted the process to be followed by the Wyeth representatives when calling on GPs. The representative had two functions, firstly to promote Zoton FasTab and secondly to offer the GastroCare Service. The product promotion part of the call was closed by means of the approved closing statement 'Is there any reason why you wouldn't start saving NOW and change all those patients on lansoprazole capsules to Zoton FasTab?'. Representatives were then to move on to the next part of the call. As part of the introduction to the service the GP was asked if they wanted to implement a proton pump inhibitor (PPI) medication review. If so the GP was asked to identify the changes they wished to be implemented and to complete the Medication Review Spreadsheet.

The Panel did not consider that the arrangements for the promotion of Zoton FasTab and the offer of the service by the representative were sufficiently separate. The discussion about Zoton FasTab concluded with a discussion about switching patients to it. The Panel considered that the subsequent introduction of a switch service by the representative would not be seen as sufficiently separate to the promotional discussions about switching to Zoton FasTab that immediately preceded it. The introduction of the service and the detailed discussion immediately after a representative had promoted Zoton FasTab meant that the service was linked to the promotion of Zoton FasTab. This would be the impression given to GPs. The role of the representative was thus unacceptable and a breach of the Code was ruled.

Upon appeal by Wyeth, the Appeal Board did not consider that the arrangements for the promotion of Zoton FasTab and the offer of the service by the representative were sufficiently separate. The GastroCare Process Flowchart showed that the closing statement of the Zoton FasTab detail was '… is there any reason why you wouldn't change your existing lansoprazole capsule patients to Zoton?'. The GastroCare Service Decision Tree told representatives that once Zoton FasTab had been fully and effectively sold and switch closed, they were to state 'Wyeth offers a simple GastroCare Service to help you achieve such medication review objectives …' (emphasis added). The material thus instructed the representative to link the offer of the service to the agreed switch to Zoton FasTab. Although the medication review spreadsheet listed the various options available the Appeal Board considered it likely that the GP would opt for the service which switched patients from lansoprazole capsules to Zoton FasTab given that that was what they had just agreed to do with the representative. In that regard no service was to be offered by the representative until the preceding product detail had been successfully closed with the doctor agreeing to switch patients to Zoton FasTabs. The Appeal Board considered that the service was in effect a way of the company ensuring that the doctor carried on what (s)he had just agreed with the representative to do. The Wyeth representatives at the appeal confirmed that a GP who decided to continue to use generic medicines would probably not be offered the service. It appeared to the Appeal Board that very few GPs had taken advantage of the GastroCare Service to do anything other than switch patients to Zoton FasTab.

The Appeal Board considered that the service was linked to the promotion of Zoton FasTab and upheld the Panel's ruling of a breach of the Code.

The Appeal Board considered that this was a serious matter; it was extremely concerned and due to what it considered was Wyeth's cynical interpretation of the Code it decided to report the company to the ABPI Board of Management in accordance with Paragraph 12.1 of the Constitution and Procedure.

During its consideration of the appeal the Appeal Board was concerned about the overall arrangements for the switch programme. The Appeal Board queried whether the switch programme was a *bona fide* medical and educational good or service which enhanced patient care or benefited the NHS as stated in the supplementary information to the Code. The Appeal Board decided that its concerns should be taken up as a separate complaint with Wyeth. This was in accordance with Paragraph 17.1 of the Constitution and Procedure. This became Case AUTH/1700/3/05.

With regard to the present case, Case AUTH/1652/11/04 the ABPI Board of Management considered that Wyeth had committed a serious breach of the Code and noted the company's submission that it found Clause 18.1 and the relevant supplementary information difficult to interpret. Whilst Wyeth appeared contrite and had signed the requisite undertaking, some members of the ABPI Board considered that emphasis had been placed on compliance with the letter of the Code as opposed to its spirit. The ABPI Board also noted inconsistencies in Wyeth's submissions to the Panel and the Appeal Board.

The ABPI Board decided that an audit should be conducted of the company's procedures and on receipt of the audit report it would consider whether further action such as a public reprimand was warranted. The new service should be examined as part of the audit.

On receipt of the audit report the ABPI Board noted the comments made in it and the steps taken and to be taken by Wyeth to address these. Taking all the circumstances into account the ABPI Board decided that a re-audit should be conducted of the company's procedures.

The ABPI Board considered that the re-audit report and Wyeth's comments upon it showed that progress had been made. Nonetheless this was a serous matter and there was still some uncertainty about training, the role of nurses and certification. The ABPI Board considered that Wyeth should be re-audited in about nine months to ensure that the progress made was maintained.

COMPLAINT

During its consideration of Case AUTH/1606/7/04 which involved a complaint from a general practitioner about a switch programme run by Wyeth Pharmaceuticals in relation to an alleged breach of the undertaking given in Case AUTH/1561/3/04, the Panel decided that certain matters, not the subject of the complaint, be taken up with Wyeth in accordance with Paragraph 17 of the Constitution and Procedure.

Case AUTH/1561/3/04

When considering Case AUTH/1606/7/04, the Panel noted that an earlier case, Case AUTH/1561/3/04 concerned the Formulary Based Implementation (FBI) Service whereby patients on Zoton capsules were switched dose for dose to the less expensive Zoton FasTab with Wyeth providing, and paying for, personnel to effect that switch. The provision of the FBI Service by Wyeth would benefit a practice by saving it the expense of carrying out the switch itself. The arrangements amounted to a pecuniary advantage given as an inducement to prescribe Zoton FasTab. Breaches of the Code had been ruled.

Case AUTH/1606/7/04

The Panel had noted that there were differences between the switch programme at issue in Case AUTH/1561/3/04 and the service at issue in Case AUTH/1606/7/04; the service was not now restricted to a switch from Zoton capsules to Zoton FasTab but was available for any oral proton pump inhibitor (PPI) of the doctor's choice.

The Panel considered the revised service only in relation to the alleged breach of undertaking. The Panel considered that the service at issue was sufficiently different from that considered in Case AUTH/1561/3/04; the service was no longer restricted to switches from Zoton capsules to Zoton FasTab but was available for all oral PPIs. The Panel considered there was no breach of the undertaking previously given. The Panel had therefore ruled no breach of Clause 22. It thus followed there was no breach of Clauses 2 or 9.1.

During its consideration of this case the Panel was concerned about the arrangements for the implementation of the revised service in relation to the requirements of Clause 18.1. The Panel noted that it had no complaint before it in this regard. The Panel was particularly concerned about the role of the representative and the representatives' briefing instructions.

The Panel noted the supplementary information to Clause 18.1 Provision of Medical and Educational Goods and Services, Section 1(ii), stated that 'If medical/generic representatives provide, deliver or demonstrate medical and educational goods and services then this must not be linked in any way to the promotion of products'. The Panel noted that the presentation to regional business managers advised representatives to promote GastroCare in full in the same call as Zoton FasTab provided … 'Zoton FasTab has been fully & effectively sold with the approved closing statements for product use and change' and 'No product promotion takes place during GastroCare Service promotion/discussion'.

The GastroCare Process Flow Chart instructed representatives during the Zoton FasTab part of the call to ask '… is there any reason why you wouldn't change your existing lansoprazole capsule patients to Zoton?'. Representatives were then asked to explain that Wyeth provided a single GastroCare service to achieve such medication review objectives. The representative would then introduce the service referring to the medication review table which showed the various PPI options. Health professionals were to indicate which ones they wanted to implement. The representative could then talk about the appropriate methods since the method of implementation differed depending on the PPI prescribing decision. Following this the doctor was to complete and sign the medication review.

The Panel noted that in its submission Wyeth stated that the prescribing decision of the GP was made in writing in advance of the offer of the service to assist in implementing the decision. It was unclear how this would work in practice; GPs would surely not complete the company's medication review form other than in relation to the provision of a service. Wyeth's submission on this point was also inconsistent with the GastroCare Process Flow chart. The Panel queried whether the role of the representative in the provision of the service met the

requirements of the supplementary information to Clause 18.1. The representative promoted Zoton FasTab and the service was introduced, according to the Flow chart, after the representative had promoted a switch from lansoprazole capsules to Zoton FasTab. The Panel was concerned that the role of the representative in relation to the service was linked to the promotion of Zoton FasTab and this would be the impression given to GPs. The Panel decided to take up its concerns as a separate complaint with Wyeth. This was in accordance with Paragraph 17.1 of the Constitution and Procedure.

RESPONSE

Wyeth accepted that the GastroCare Process Flow Chart which suggested that the instruction to ask '… is there any reason why you wouldn't change your existing lansoprazole capsule patients to Zoton FasTab?' was closely linked to, and a first step, in the process of offering the GastroCare Service. This was not the case and not intended and Wyeth accepted that if it was the case a breach of Clause 18.1 could be argued. It was happy to amend the GastroCare Process Flow Chart to remove this first step and to give an undertaking in this regard.

Wyeth stated that the position was in fact as set out in the presentation to regional business managers which advised that representatives could introduce the GastroCare Service in a clearly distinct and separate part of the same GP call as the promotion of Zoton FasTab provided no product promotion took place during the GastroCare Service discussion. Wyeth maintained that this position was acceptable and did not breach Clause 18.1 and accordingly did not propose to change this practice.

In response to a request for further information about the implementation of the revised switch service Wyeth noted the Panel's concerns over the role of the representative in introducing the service during the same call as a related Wyeth product had been promoted and the briefing given to representatives in relation to this.

Wyeth stated that its GastroCare Service offered to GPs was non-brand specific and could be offered and performed in respect of any relevant 'brand' of gastrointestinal medication (ie proprietary or generic) of the GP's choice. Wyeth offered this service as a medical service that would enhance patient care and benefit the NHS. The supplementary information to Clause 18.1 indicated that this clause did not prevent the provision of such services provided that they were not done in such a way as to be an inducement to prescribe any medicine. Wyeth had considered the requirements of Clause 18.1 and the associated guidance with care in order to be satisfied that it complied with the Code and that it could provide this valuable service to the NHS.

Documents setting out the details of the service, training and representatives' briefing material were provided by Wyeth.

Briefly, the GP was asked to indicate the PPI medication review they wished to implement by completing and signing the Medication Review Spreadsheet. If the GP only wanted to change prescribing from one formulation of a PPI to another formulation of the same PPI in a dose for dose switch, then in order to assist the GP in implementing that prescribing decision the representative offered the GP Systems Specialist Implementation (GPSSI) service, using the GPSSI Pack (ZZOT3588). If the GP accepted the service offering, the Practice Booking and Consent Form was completed by the GP and the representative arranged an external supplier to carry out the service at the practice.

If, however, the GP wanted to change a patient to another PPI or to another dose, then a full audit and review was needed and an appointment would be arranged for a GastroCare Specialist to explain to the GP the service to be provided, to obtain all appropriate consents of the GP for this service to be provided and then to organise a convenient time for the audit and review to take place.

Wyeth's process permitted the representative to take the above steps in a part of their call on the GP that was clearly separated from any product promotion. In making the two discussions distinct and separate, in Wyeth's view there was no link between the promotion of Wyeth's Zoton FasTabs and the service offering. Further, in any event, Wyeth did not consider that the implementation of the service was in breach of Clause 18.1 for the following reasons:

1 There was clear separation of product promotion from the offer of the GastroCare Service.

The need for this had been reinforced to representatives in a number of ways including by the regional business managers (RBMs) as part of a workshop at their quarterly management meeting held in June 2004 (their presentation included a section on the outcome of the Zoton FasTab promotion complaint and a description of the new revised service offering, plus a clear reminder regarding the product and service separation aspect (ZZOT3589)); in the GastroCare GP Systems Specialist and Audit Review Service Representative Briefing Document (ZZOT3581); through the Action Plan (ZZOT3580); through the GastroCare Process Flowchart (ZZOT3601) – this started with an instruction for the representative to close the product call before commencing any discussion relating to service; and through verbal reinforcement of the message by the RBMs when passing this information to the representatives.

2 The product promotion part of the call was closed by the use of the approved closing statement 'Is there any reason why you wouldn't start saving NOW and change all those patients on lansoprazole capsules to Zoton FasTab?'

3 Having closed the PPI promotion part of the call, the representative would then move on to the next part of their call. It was common practice for a representative to deal with more than one item in a GP call, such as detailing more than one product. The representative was detailing to a highly intelligent GP, well used to dealing with more than one issue in the same visit and to separate out different product promotion and indeed a service offering.

4 The material used by the representative and the training given on the material was very clear in identifying that the GastroCare Service was a service offered to implement the GP's PPI prescribing decisions – whatever they were. The service could be used to implement any PPI prescribing decision of the GP, whether or not it had resulted from the promotion given by the representative.

5 The new material, and the material use sequence, made it clear that the GP's prescribing decision must be made in advance of any offer of a service to assist in implementing that decision. In doing so, Wyeth sought to ensure that there was no inducement to make a prescribing decision when the service offering was made.

6 As a part of the introduction to the service, the GP was asked if they wanted to implement a PPI medication review. If the GP said yes they were asked to identify the PPI changes they wished to be implemented and to complete the Medication Review Spreadsheet. Notwithstanding that indicating the prescribing decision was to be made in advance of the GastroCare Service being offered, it was made clear that the medication review was available to implement any PPI change requested by the GP (ie whether in relation to Wyeth's product or that of a competitor). The full list of PPIs was identified, and a blank spreadsheet was available for the GP to complete and the GP had a free choice here. The Medication Review Spreadsheet was used because the method of review was dependent on the PPI change to be undertaken and so would govern the type of service that the GP would be provided further details on – either by the representative or a specialist in a follow-up visit.

In previous responses it had been indicated that Wyeth required the prescribing decision to be made in writing in advance of the service offering and implied that this was done by completion of the Medication Review Spreadsheet. In fact this was not the case and the spreadsheet completion was part of the service offering part of the call.

The GastroCare Process Flowchart, used only as part of the initial representative training included as a first step the 'Zoton FasTab "Tell, Tell, Tell" detail and close' which Wyeth now recognised could be misunderstood to indicate that this was part of the GastroCare Service offering process and implied a link between the two. The inclusion of this statement was intended only to demonstrate that the promotional part of the call must be closed before the service part of the call was commenced. It was clear from all other documents used that it was a key requirement that any product promotion was closed and stopped before any service offering was introduced and made.

The Panel had noted the supplementary information to Clause 18.1 Provision of Medical and Educational Goods and Services, Section 1(ii) which stated 'If medical/generic representatives provide, deliver or demonstrate medical and educational goods and services then this must not be linked in any way to the promotion of products'. In the case of the GastroCare Service, Wyeth's medical/generic representatives were neither providing, delivering nor demonstrating medical and educational goods and services. They were simply making GPs aware of the service offering to facilitate its implementation by other non-medical/generic representatives.

A ruling of a breach of Clause 18.1 required a finding that the company had induced the GP to buy, procure or prescribe a medicine. Wyeth strongly argued that this was not the case here and did not accept that the offer of the service was inducing the prescribing decision made by the GP in advance of the service offering. If the GP identified different or further prescribing decisions following the service offering, was it inducing those too – including any decisions to prescribe a competitor PPI? Further, as the GP had a free hand in choosing the PPI medication review to be implemented, how was it that the service offering was inducing the prescribing decision?

Wyeth provided a service that was much needed by the NHS and GP practices – a service where the GP could implement the PPI prescribing decisions they made – whatever they were – and so meet best practice quickly for the benefit of the patient.

Therefore for the reasons indicated above, Wyeth believed that its practice of offering the GastroCare Service in the same call as its product promotion, did not induce the GP to prescribe a specific medicine and was therefore not in breach of Clause 18.1.

PANEL RULING

The Panel noted the various matters identified and taken up as a complaint with Wyeth under Paragraph 17 of the Constitution and Procedure. The Panel noted that Wyeth had agreed to withdraw the GastroCare Process Flow Chart. The Panel noted that, as previously explained to Wyeth, the matter taken up under Paragraph 17 related to the Panel's concerns about the cumulative effect of the arrangements regarding the role of the representative and the impression given to GPs and this remained before it for consideration.

The Panel noted that Wyeth maintained that its representatives could introduce the service in a clearly distinct and separate part of the same GP call as the promotion of Zoton FasTab provided no product promotion took place during the GastroCare service discussion.

The Panel noted the process to be followed by the Wyeth representatives when calling on GPs. The representative had two functions, firstly to promote Zoton FasTab and secondly to offer the GastroCare Service. The product promotion part of the call was closed by means of the approved closing statement 'Is there any reason why you wouldn't start saving NOW and change all those patients on lansoprazole capsules to Zoton FasTab?'. Representatives were then to move on to the next part of the call. As part of the introduction to the service the GP was asked if they wanted to implement a PPI medication review. If so the GP was asked to identify the changes they wished to be implemented and to complete the Medication Review Spreadsheet. The Panel noted Wyeth's submission that previously it had stated that the prescribing decision was made in writing in

advance of the service offering and this was done by completion of the Medication Review Spreadsheet. Wyeth now stated that this was not so and the spreadsheet completion was part of the service offering part of the call. The Panel was extremely concerned that Wyeth had changed its submission. Further it was not clear whether Wyeth's latest submission meant that the prescribing decision was not made in writing in advance of the service offering or that the prescribing decision was not made in writing by means of completion of the Medication Review Spreadsheet.

The GastroCare Process Flowchart instructed representatives to sell Zoton FasTab and close. The flowchart used the example '…is there any reason why you wouldn't change your existing lansoprazole capsule patients to Zoton'. The next part of the flowchart stated 'Wyeth offers a single GastroCare service to help you achieve such medication review objectives'. The flowchart used the example 'This Medication Review table shows the various PPI options. If you indicate which ones you want to implement, I can then talk about the appropriate method to do that, since the method of implementation differs depending on the PPI prescribing decision'. The flowchart then stated 'Doctor(s) completes and signs the Medication Review'. This was accompanied by the instruction that representatives were not allowed to influence the doctor during the discussion on medication review. The flowchart then instructed the representatives to offer the most appropriate part of the service relevant to the completed medication review. Reference was made to the GastroCare Service Decision Tree.

The GastroCare Service Decision Tree instructed representatives that 'Once Zoton FasTab has been fully and effectively sold and switch closed…' followed by a box containing 'Wyeth offers a single GastroCare service to help you achieve such medication review objectives. This Medication Review table shows the various PPI options. If you indicate which ones you want to implement, I can then talk about the appropriate method to do that since the method of implementation differs depending on the PPI prescribing decision'. Three possible options were outlined. Firstly PPI change of formulation only, secondly any PPI medicine change and thirdly any PPI dose change.

The Panel noted the supplementary information to Clause 18.1 of the Code that the provision of medical and educational goods and services which would enhance patient care and benefit the NHS was not prevented by Clause 18.1. The provision of such goods or services must not be done in such a way as to be an inducement to prescribe, supply, administer, recommend or buy any medicine. The Panel also noted the advice that if representatives provided, delivered or demonstrated medical and educational goods and services then this must not be linked in any way to the promotion of medicines.

The Panel did not consider that the arrangements for the promotion of Zoton FasTab and the offer of the service by the representative were sufficiently separate. The discussion about Zoton FasTabs concluded with a discussion about switching patients to it. The Panel considered that the subsequent introduction of a switch service by the representative would not be seen as sufficiently separate to the promotional discussions about switching to Zoton FasTabs that immediately preceded it. The introduction of the service and the detailed discussion immediately after a representative had promoted Zoton FasTab meant that the service was linked to the promotion of Zoton FasTab. This would be the impression given to GPs. The role of the representative was thus unacceptable in relation to the requirements of Clause 18.1; a breach of Clause 18.1 was ruled.

APPEAL BY WYETH

Wyeth considered that the Panel's ruling had not related to the detail of the GastroCare Service itself, only to the arrangements for its introduction to GPs and the role of the representative in relation to this. Accordingly, this appeal related to the Panel's findings on this aspect of the arrangements.

Wyeth appealed primarily to seek greater clarity on how its approach to offering the GastroCare Service **induced** a health professional to prescribe a medicine. If it did not, and Wyeth did not consider that it did, then it was not in breach of Clause 18.1 of the Code. However, if the Appeal Board agreed with the Panel and found that it did, then Wyeth considered that clarity on exactly how the inducement arose, and what would be acceptable in making future service offerings, was critical not only for Wyeth but also for other pharmaceutical companies and health professionals.

Wyeth did not consider that the Panel's ruling was sufficiently clear as to its reasoning. Without clarity Wyeth could not be certain that it had made the necessary changes to its future arrangements to ensure they did not breach Clause 18.1 and did not breach any undertaking given in relation to this case. Also, health professionals offered the GastroCare Service in the future would continue to look to the Authority to help them assess whether any revised service implementation was acceptable.

Wyeth sought clarity on the Panel's ruling from the Authority and was advised that it could provide no further clarity and if this was needed it should be sought through an appeal. Wyeth was committed to compliance and offering only services that met the requirements of Clause 18.1. Wyeth therefore appealed.

Wyeth's position was as follows:

1 It was acceptable for a medical representative to inform GPs about a medical service available from Wyeth and to offer this to GPs.

2 The supplementary information to Clause 18.1 stated that it could be acceptable for medical representatives to be involved in providing, delivering and demonstrating medical services but in the company's view that was not what Wyeth was concerned with here. Instead it was concerned with a step before that where the service itself was not being provided, delivered or demonstrated; it was being introduced and offered.

3 Accordingly, this part of the guidance in the supplementary information to Clause 18.1 was useful and informative, and much of it was useful in considering the role of the representative in offering services, but Wyeth disagreed with the way that the Panel had used the supplementary information in its ruling as the test for acceptability of the role of the representative in the offer of the service.

4 Instead, Wyeth submitted that the wording of Clause 18.1 remained key and so it must be decided whether the role and arrangements of the representative were such that a gift, benefit in kind or pecuniary advantage was being offered to members of the health profession as an inducement to prescribe any medicine. In other words, whether the arrangements were such that the service was being offered to persuade the GP to prescribe a medicine.

5 Wyeth accepted that if there was a link between the offer of a service and the promotion of a product, then at first sight this suggested that the offer of the service was being made to induce a prescription of the promoted product.

6 Wyeth submitted that its arrangements for the offer of the GastroCare Service had broken the link between the promotion of the product and the service offered – both the material itself and the instructions and training given to representatives made it very clear that this must be the case.

7 Conversely the Panel did not consider that the promotion of Zoton FasTab and the offer of the service by the representative were sufficiently separate. The Panel's ruling indicated that this was because the discussion about Zoton FasTab concluded with a discussion about switching patients to it and so the subsequent introduction of a switch service by the representative would not be seen as sufficiently separate to the promotional discussion that immediately preceded it.

8 However, what the representative introduced after the promotion of Zoton FasTab was not just the offer of a switch service, it was the offer of services relating to a PPI review and a switch service was only one of the available services. The exact service discussed was directed by the prescriber's stated prescribing preference not by the representative. The offer of a PPI formulation change service, for example, was only one of the services that could then be offered based on the stated prescribing preference; another could be a full review of PPI prescribing and patient management.

9 Wyeth had designed the service in this way to ensure that it could talk about the specific service that met the needs of the prescriber (as communicated to the representative by the prescriber on the Medication Review Spreadsheet) but importantly also so the service offering was not seen as inducing a prescribing decision. The prescribing decision was taken in advance of the detailed service offering and so the company did not see how it could be induced (persuaded or caused) by it. How could a subsequent offer cause a prior event to happen?

10 The Medication Review Spreadsheet enabled the prescriber to record their prescribing decision. The Panel indicated concern that Wyeth had changed its description of how and when this form was used. The position was that the form was used as part of the service discussion, but at the very start of it before any offer of a service was given. This had meant that the offer of a service under the GastroCare Service was given only after first identifying with the doctor what prescribing decision they were interested in implementing. In this way, the doctor had indicated his/her prescribing decision before the relevant service was offered. Again, Wyeth did not see how the prescribing decision could be induced by the offer of the service. How could a subsequent offer cause a prior event to happen?

11 It was clear that the Panel considered there was a breach of Clause 18.1 because it considered that the promotion of the product and the service offering were linked, as one followed the other and that this would give the impression of linkage to the doctor.

What was not clear at all from the Panel's ruling was whether this was the critical reason it considered there was a 'link', and so in its view a breach, and importantly what would be sufficient to break that link or avoid a breach. If the discussions were separated by a different product detail, would the arrangements still be in breach of Clause 18.1? If the discussions took place in separate visits on separate days, would they be in breach of Clause 18.1? What if the doctor indicated that they did not want separation, (s)he had made a prescribing decision and wanted to know if Wyeth had any services it could offer to help implement it? It was clear that in such circumstances the offer of a service was not inducing the prescribing decision as no such offer had been made. Was a response to the doctor's request a breach of Clause 18.1 and if so why?

Wyeth submitted that this appeal was driven primarily by a desire for clarity on the arrangements that were acceptable. If Wyeth's arrangements set out in its material were not acceptable, it was important that this decision gave guidance as to precisely why and what would be acceptable. Wyeth noted that its response to the original complaint had sought this but the Panel ruling gave no such guidance. The ruling contained just one paragraph identifying in brief terms why the ruling of a breach was given and with the reason possibly being that it was only because one discussion immediately followed the other. If this was the case, and some separation would have meant the arrangements were acceptable, then Wyeth asked the Appeal Board to clarify this for all.

In conclusion, Wyeth appealed the ruling of a breach of Clause 18.1. If the Appeal Board's decision, however, was to uphold the Panel's ruling, then Wyeth asked for clarity to be given as to what it was about its arrangements that gave rise to an inducement to prescribe and what should be done to avoid this in the future.

APPEAL BOARD RULING

The Chairman informed the Wyeth representatives that the Appeal Board's role was not to give guidance or advice as to how to comply with the Code.

The Appeal Board noted Wyeth's submission at the appeal hearing that the 'Panel did not find services offered unacceptable'. This was incorrect. The Appeal Board noted that the Panel had not considered the acceptability of the overall arrangements in relation to Clause 18.1. Case AUTH/1652/11/04 had concerned the role of the representative in relation to the revised service.

The Appeal Board noted that the supplementary information to Clause 18.1 of the Code stated that the provision of medical and educational goods and services which would enhance patient care and benefit the NHS was not prevented by Clause 18.1. The provision of such goods or services must not be done in such a way as to be an inducement to prescribe, supply, administer, recommend or buy any medicine. The Appeal Board also noted the advice that if representatives provided, delivered or demonstrated medical and educational goods and services then this must not be linked in any way to the promotion of medicines.

The Appeal Board did not consider that the arrangements for the promotion of Zoton FasTab and the offer of the service by the representative were sufficiently separate. The GastroCare Process Flowchart showed that the closing statement of the Zoton FasTab detail was '… is there any reason why you wouldn't change your existing lansoprazole capsule patients to Zoton?'. The GastroCare Service Decision Tree told representatives that once Zoton FasTab had been fully and effectively sold and switch closed, they were to state 'Wyeth offers a simple GastroCare Service to help you achieve such medication review objectives …' (emphasis added). The material thus instructed the representative to link the offer of the service to the agreed switch to Zoton FasTab. Although the medication review spreadsheet listed the various options available the Appeal Board considered it likely that the GP would opt for the service which switched patients from lansoprazole capsules to Zoton FasTab given that that was what they had just agreed to do with the representative. In that regard no service was to be offered by the representative until the preceding product detail had been successfully closed with the doctor agreeing to switch patients to Zoton FasTabs. The Appeal Board considered that the service was in effect a way of the company ensuring that the doctor carried on what (s)he had just agreed with the representative to do. The Wyeth representatives at the appeal confirmed that a GP who decided to continue to use generic medicines would probably not be offered the service. It appeared to the Appeal Board that very few GPs had taken advantage of the GastroCare Service to do anything other than switch patients to Zoton FasTab.

The Appeal Board considered that the introduction of the service and the detailed discussion immediately after a representative had successfully closed a Zoton FasTab detail meant that the service was linked to the promotion of Zoton FasTab. This would be the impression given to GPs. The role of the representative was thus unacceptable in relation to the requirements of Clause 18.1. The Appeal Board upheld the Panel's ruling of a breach of Clause 18.1. The appeal on this point was unsuccessful.

The Appeal Board considered that this was a serious matter; it was extremely concerned about what it considered was Wyeth's cynical interpretation of the requirements of Clause 18.1 and, as a consequence, decided to report the company to the ABPI Board of Management in accordance with Paragraph 12.1 of the Constitution and Procedure.

* * * * *

During its consideration of the appeal the Appeal Board was concerned about the overall arrangements for the switch programme in relation to the requirements of Clauses 2, 9.1 and 18.1 of the Code. The Appeal Board noted that it had no complaint before it in this regard.

The Appeal Board queried whether the switch programme was a *bona fide* medical and educational good or service which enhanced patient care or benefited the NHS as stated in the supplementary information to Clause 18.1 Provision of Medical and Educational Goods and Services.

The Appeal Board decided that its concerns should be taken up as a separate complaint with Wyeth. This was in accordance with Paragraph 17.1 of the Constitution and Procedure. (Case AUTH/1700/3/05).

* * * * *

CONSIDERATION BY THE ABPI BOARD OF MANAGEMENT

The ABPI Board of Management considered that Wyeth had committed a serious breach of the Code and noted the company's submission that it found Clause 18.1 and the relevant supplementary information difficult to interpret. Whilst Wyeth appeared contrite and had signed the requisite undertaking, some members of the ABPI Board considered that emphasis had been placed on compliance with the letter of the code as opposed to its spirit. The ABPI Board also noted inconsistencies in Wyeth's submissions to the Panel and the Appeal Board.

During a wide ranging discussion the ABPI Board considered the applicable options which included taking no further action, conducting an audit and/or issuing a reprimand or corrective statement.

The ABPI Board decided that an audit should be conducted of the company's procedures and on receipt of the audit report the ABPI Board would consider whether further action such as a public reprimand was warranted. The new service should be examined as part of the audit.

FURTHER CONSIDERATION BY THE ABPI BOARD OF MANAGEMENT

The ABPI Board considered the audit report and Wyeth's comments upon it.

The ABPI Board noted the comments made in the audit report and the steps taken and to be taken by

Wyeth to address these. The ABPI Board considered this was a serious matter. Taking all the circumstances into account the ABPI Board decided that a re-audit should be conducted of the company's procedures. On receipt of the audit report the ABPI Board would consider whether further action was warranted.

FURTHER CONSIDERATION BY THE ABPI BOARD OF MANAGEMENT

The ABPI Board considered the re-audit report and Wyeth's comments upon it. The ABPI Board considered that this was a serious matter. Wyeth had made progress. There was still some uncertainty about training, the role of nurses and certification. The ABPI Board considered that Wyeth should be re-audited in about nine months (September 2006) to ensure that the progress made was maintained.

Proceedings commenced **21 October 2004**

PMCPA proceedings completed **4 April 2005**

Case completed **22 December 2005**

CASE AUTH/1659/11/04

PRIMARY CARE TRUST MEDICINES MANAGEMENT SUPPORT PHARMACIST/DIRECTOR v WYETH

Breach of undertaking

A medicines management support pharmacist at a primary care trust (PCT) complained about a letter from Wyeth which discussed switching from Zoton capsules to Zoton FasTab. The complainant referred to an article in the BMJ, 26 June which discussed a previous case, Case AUTH/1561/3/04, wherein Wyeth was ruled in breach of the Code for offering a service which switched patients on Zoton (lansoprazole) capsules to Zoton FasTab.

As the case involved an alleged breach of undertaking it was taken up by the Director as it was the responsibility of the Authority to ensure compliance with undertakings. This accorded with advice previously given by the Appeal Board.

The complainant stated that individuals within his PCT had received letters dated 25 October 2004 from Wyeth in which it offered to provide support to implement a change from lansoprazole capsules to Zoton FasTab in GP practices. The complainant telephoned the person given as the contact in the letter to enquire what this support entailed and was told that Wyeth could provide technicians or nurses to GP practices to carry out this change.

As far as the complainant could see this was in direct contravention of the ruling that such practice breached the Code and Wyeth's own undertaking to suspend this activity, as reported in the BMJ article, 26 June.

The Panel noted that the previous case, Case AUTH/1561/3/04, concerned the formulary based implementation (FBI) Service whereby patients on Zoton capsules were switched to Zoton FasTab. The Panel had considered that the FBI Service was part of the promotion of Zoton FasTab. The service could thus not benefit from the supplementary information to the Code regarding the provision of medical and educational goods and services. The provision of the FBI Service by Wyeth would benefit a practice by saving it the expense of carrying out the switch itself. The arrangements amounted to a pecuniary advantage given as an inducement to prescribe Zoton FasTab. Breaches of the Code had been ruled.

Turning to the present case, Case AUTH/1659/11/04, the Panel noted that the letter at issue began by stating that the prices of Zoton and Zoton FasTab had changed. The letter noted that the price of Zoton capsules had increased by 7% and discussed the cost savings that could be achieved within that PCT by switching formulation from Zoton capsules to Zoton FasTab and implementing a maintenance dose reduction program. The letter concluded by stating that the capsule and FasTab formulations were bioequivalent and that Wyeth could provide support to help implement these formulation and/or dose changes. The reader was invited to telephone Wyeth's local healthcare development manager to discuss how Wyeth could help implement these changes.

The Panel noted the complainant's submission that the Wyeth support entailed the provision of technicians or nurses to GP practices to carry out this change. Wyeth had not responded on this point. The Panel noted Wyeth's submission that it no longer had such a limited service as described in the letter; this had been replaced with an implementation service based on the full range of proton pump inhibitor (PPI) prescribing decisions.

The Panel considered that the letter at issue offered support to switch from Zoton capsules to Zoton FasTab and was thus in breach of the undertaking given in Case AUTH/1561/3/04. A breach of the Code was ruled as accepted by Wyeth. High standards had not been maintained. A breach of the Code was ruled.

The Panel noted that the letter was developed and prepared in March 2004. Wyeth was advised of the Panel's rulings in Case AUTH/1561/3/04 on 23 April; the form of undertaking, which included an assurance to take all possible steps to avoid similar

breaches of the Code in the future was dated 7 June. The letter at issue, however, remained in use. The fact that the letter referred to a service which had been ruled in breach of the Code was not spotted when materials were reviewed in the light of Case AUTH/1561/3/04 or when it was reviewed in August 2004 and amended to reflect the new price of the medicines. The Panel considered that this was a serious matter; the letter ought to have been withdrawn pursuant to the undertaking in Case AUTH/1561/3/04 but was instead used for a further five months. It appeared that no thought had been given to the acceptability of the material either when the undertaking was provided or when the letter was amended in August 2004. The healthcare development manager named in the letter had not taken into account the previous ruling. The Panel was concerned about Wyeth's submission that the letter had not been withdrawn because the offer of support to switch from Zoton capsules to Zoton FasTab was not its purpose. Wyeth should have procedures in place to ensure that all material which referred to the activity at issue was withdrawn irrespective of its primary purpose. Action had only been taken on receipt of the present complaint. This was unacceptable. The Panel considered that the circumstances brought discredit upon and reduced confidence in the pharmaceutical industry; a breach of Clause 2 was ruled which was appealed by Wyeth.

The Panel noted that the BMJ article about Case AUTH/1561/3/04 had raised the profile of Wyeth's activities amongst health professionals with regard to Zoton and Zoton FasTab. The Authority had subsequently received a number of complaints about the revised switch service some of which referred to the article in the BMJ. In responding to those complaints which concerned an alleged breach of the undertaking given in Case AUTH/1561/3/04, Wyeth had stated on each occasion that it had fully complied with the undertaking given. This submission was incorrect. As a result of the present case, Case AUTH/1659/11/04 it was apparent that Wyeth had not withdrawn all of the material at issue. The continued use and even amendment of the letter at issue to include up-to-date prices was totally unacceptable. The Panel decided to report Wyeth to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

The Appeal Board noted that the originator of the August letter had not been briefed on the outcome of Case AUTH/1561/3/04, or subsequent cases which concerned an alleged breach of the undertaking given in Case AUTH/1561/3/04 concerning Wyeth's switch programmes. The Appeal Board considered that this was unacceptable. It noted, with concern, that the letter had been signed off by a signatory familiar with Case AUTH/1561/3/04 and the subsequent cases which concerned the alleged breach of undertaking. Overall, the Appeal Board considered that Wyeth had brought discredit upon and reduced confidence in the Pharmaceutical Industry and so it upheld the Panel's ruling of a breach of Clause 2. The appeal on this point was unsuccessful.

In relation to the report the Appeal Board noted that following Case AUTH/1561/3/04 there had subsequently been a number of complaints about the revised switch service. In responding to those complaints which concerned an alleged breach of the undertaking given in Case AUTH/1561/3/04, Wyeth had stated on each occasion that it had fully complied with the undertaking given. This submission was incorrect. After Case AUTH/1606/7/04, successive allegations of a breach of the undertaking in Case AUTH/1561/3/04 had not triggered further reviews of materials. As a result of the present case, Case AUTH/1659/11/04, it was apparent that Wyeth had not withdrawn all of the material at issue. The Appeal Board decided that, within the next month, Wyeth should be required to undergo a compulsory audit of its procedures relating to the Code as set out in Paragraph 10.4 of the Constitution and Procedure. Following receipt of the audit report the Appeal Board would then consider whether further action was necessary.

Upon receipt of the report on the audit, the Appeal Board noted that it had reported Wyeth to the ABPI Board of Management in relation to Case AUTH/1652/11/04. The ABPI Board of Management had decided that Wyeth should undergo an audit. This would be carried out soon so that the ABPI Board could consider the matter at its next meeting in September.

The Appeal Board decided that further action in Case AUTH/1659/11/04 was needed. It requested sight of the report for the audit required by the ABPI Board of Management in relation to Case AUTH/1652/11/04. The Appeal Board decided to defer consideration until that had been established. Nonetheless it decided that Wyeth should be re-audited in about nine months' time.

A medicines management support pharmacist at a primary care trust (PCT) complained about a letter (ref ZZOT3656/0304) from Wyeth Pharmaceuticals which discussed switching from Zoton capsules to Zoton FasTab. The letter was signed by the Sales and Marketing Director – Primary Care. The complainant referred to an article in the BMJ, 26 June which discussed a previous case, Case AUTH/1561/3/04, wherein Wyeth was ruled in breach of the Code for offering a service which switched patients on Zoton (lansoprazole) capsules to Zoton FasTab.

As the case involved an alleged breach of undertaking it was taken up by the Director as it was the responsibility of the Authority to ensure compliance with undertakings. This accorded with advice previously given by the Appeal Board.

COMPLAINT

The complainant stated that individuals within his PCT had received letters dated 25 October 2004 from Wyeth in which it offered to provide support to implement a change from lansoprazole capsules to Zoton FasTab in GP practices. The complainant telephoned the person indicated in the letters to enquire what this support entailed and was told that Wyeth could provide technicians or nurses to GP practices to carry out this change. As far as the

complainant could see this was in direct contravention of the ruling that such practice breached the Code and Wyeth's own undertaking to suspend this activity, as reported in the BMJ article of 26 June.

Anecdotally the complainant had heard from another PCT that Wyeth had been continuing this activity in at least one of its GP practices.

When writing to Wyeth, the Authority asked it to respond in relation to Clauses 2, 9.1 and 22.

RESPONSE

Wyeth explained that the letter at issue was sent to primary care organisation (PCO) chief executives, finance directors, public health directors or similar PCO senior managers to highlight the cost savings available in their PCO if they were to implement a lansoprazole formulation change and/or a lansoprazole dose reduction program. This letter was developed and prepared in March 2004 for this purpose.

The references made to the support Wyeth could provide to help implement these changes were to the proton pump inhibitor (PPI) prescribing review programmes Wyeth had available from time to time. Originally, this would have included the Formulary Based Implementation (FBI) service that had been withdrawn following the ruling in Case AUTH/1561/3/04. Now it was to the Wyeth GastroCare service which offered support for the implementation of a wide range of PPI prescribing decisions at the option and direction of the prescriber.

When reviewing Wyeth's promotional and service material in the light of Case AUTH/1561/3/04, the references made in these letters to the support Wyeth could offer were not picked up and consequently did not receive amendment or deletion at the time. Whilst the letters were updated in August 2004 this was done solely to reflect the change in price of the Zoton products available and again the references were not identified in this review. Wyeth confirmed that the letter was certified in accordance with Clause 14 of the Code.

Notwithstanding the reference in the letter to the support to implement the formulation and/or dose changes, Wyeth no longer provided such a limited service as described in the letter. Wyeth only had a service which supported the implementation of the PPI prescribing preferences of the directing prescriber based on the full range of PPI prescribing choices made available to them. In effect the letter made references to support that could not be met in the terms stated and was, accordingly, out of date.

Wyeth recognised that the letter gave the impression that support could be provided for a switch to a specific medicine. Wyeth had withdrawn that support and had taken significant steps to ensure that reference to it was no longer made in its material. The reference in the letter identified by the complainant was missed as it was not the purpose of the letter and Wyeth recognised it should no longer be there. Immediately this oversight was identified to Wyeth it withdrew the letter from use. Wyeth had sent more than 200 such letters to senior PCO managers.

By missing this reference in this letter, Wyeth accepted that it had not maintained high standards. However, Wyeth did not consider it had brought discredit or reduced confidence in the pharmaceutical industry by its actions.

PANEL RULING

The Panel considered that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in the future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted that the previous case, Case AUTH/1561/3/04, concerned the FBI service whereby patients on Zoton capsules were switched to Zoton FasTab. The Panel had considered that the FBI Service was part of the promotion of Zoton FasTab; it was not described as anything else in the material. The service could thus not benefit from the supplementary information to Clause 18.1 regarding the provision of medical and educational goods and services. The provision of the FBI Service by Wyeth would benefit a practice by saving it the expense of carrying out the switch itself. The arrangements amounted to a pecuniary advantage given as an inducement to prescribe Zoton FasTab. Breaches of Clauses 9.1 and 18.1 had been ruled.

Turning to the present case, Case AUTH/1659/11/04, the Panel noted that the letter at issue began by stating that the prices of Zoton and Zoton FasTab had changed. The letter noted that the price of Zoton capsules had increased by 7% and discussed the cost savings that could be achieved within that PCT by switching formulation from Zoton capsules to Zoton FasTab and implementing a maintenance dose reduction program. The letter concluded by stating that the capsule and FasTab formulations were bioequivalent and that Wyeth could provide support to help implement these formulation and/or dose changes. The reader was invited to telephone Wyeth's local healthcare development manager to discuss how Wyeth could help implement these changes.

The Panel noted the complainant's submission about his telephone conversation with the local healthcare development manager mentioned in the letter. According to the complainant he had enquired what the support entailed and had been told that Wyeth could provide technicians or nurses to GP practices to carry out this change. Wyeth had not responded on this point. The Panel noted Wyeth's submission that it no longer had such a limited service as described in the letter; this had been replaced with an implementation service based on the full range of PPI prescribing decisions.

The Panel considered that the letter at issue offered support to switch from Zoton capsules to Zoton FasTab and was thus in breach of the undertaking given in Case AUTH/1561/3/04. A breach of Clause 22 was ruled as accepted by Wyeth. High standards had not been maintained. A breach of Clause 9.1 was ruled. These rulings were not appealed.

The Panel noted that the letter was developed and prepared in March 2004. Wyeth was advised of the Panel's rulings in Case AUTH/1561/3/04 on 23 April; the form of undertaking, which included an assurance to take all possible steps to avoid similar breaches of the Code in the future was dated 7 June. The letter at issue, however, remained in use. The fact that the letter referred to a service which had been ruled in breach of the Code was not spotted when materials were reviewed in the light of Case AUTH/1561/3/04 or when it was reviewed in August 2004 and amended to reflect the new price of the medicines. The Panel considered that this was a serious matter; the letter ought to have been withdrawn pursuant to the undertaking in Case AUTH/1561/3/04 but was instead used for a further five months. It appeared that no thought had been given to the acceptability of the material either when the undertaking was provided or when the letter was amended in August 2004. The healthcare development manager named in the letter had not taken into account the previous ruling. The Panel was concerned about Wyeth's submission that the letter had not been withdrawn because the offer of support to switch from Zoton capsules to Zoton FasTab was not its purpose. Wyeth should have procedures in place to ensure that all material which referred to the activity at issue was withdrawn irrespective of its primary purpose. Action had only been taken on receipt of the present complaint. This was unacceptable. The Panel considered that the circumstances brought discredit upon and reduced confidence in the pharmaceutical industry; a breach of Clause 2 was ruled which was appealed by Wyeth.

The Panel noted that the BMJ article about Case AUTH/1561/3/04 had raised the profile of Wyeth's activities amongst health professionals with regard to Zoton and Zoton FasTab. The Authority had subsequently received a number of complaints about the revised switch service some of which referred to the article in the BMJ. In responding to those complaints which concerned an alleged breach of the undertaking given in Case AUTH/1561/3/04, namely Cases AUTH/1606/7/04, AUTH/1617/8/04, AUTH/1629/9/04 and AUTH/1655/11/04, Wyeth had stated on each occasion that it had fully complied with the undertaking given. This submission was incorrect. As a result of the present case, Case AUTH/1659/11/04 it was apparent that Wyeth had not withdrawn all of the material at issue. The continued use and even amendment of the letter at issue to include up-to-date prices was totally unacceptable. The Panel decided to report Wyeth to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

APPEAL BY WYETH

Wyeth appealed the Panel's ruling that it had brought discredit upon, and reduced confidence in, the pharmaceutical industry by the drop in standards that had given rise to this case. Wyeth did not intend to suggest a reduction in the importance it attached to compliance with undertakings given.

The purpose of the letter in question, sent to PCO board members, was to identify potential PPI cost savings available to the recipients. The letter also briefly referred to the fact that Wyeth could provide support to help implement formulation and/or dose changes. The letter was relevant to the support services Wyeth had available at the time, but required modification following Wyeth's undertaking in Case AUTH/1561/3/04. The letter was originally developed and approved in March 2004 prior to the Panel's ruling in Case AUTH/1561/3/04 and the undertaking given in that case on 7 June 2004. Following that ruling, Wyeth withdrew all FBI service materials immediately but the reference made in this letter to the support it could provide was missed and so the letter was not withdrawn and amended. The letters were updated in August 2004 solely to reflect the change in price of the Zoton products available and the unacceptable wording was not identified in this review.

Wyeth accepted this had demonstrated a failure to maintain high standards and it had taken steps to address this. The failure to identify the inappropriate reference to the support service was a genuine error; there was no deliberate action by Wyeth to disregard the Panel's ruling and the undertaking it had given. Wyeth noted that whilst the letter stated that the company could offer support to implement the changes identified in the letter, such services were no longer available in the terms stated.

Wyeth noted, that in terms of disrepute caused to the industry by its actions, there had been only one complaint about the letter. It was notable also that the basis of the present complaint was a news item in the BMJ dated 26 June 2004, which incorrectly stated that Wyeth had suspended its audit programme, whereas in reality the programme continued following modification. The complainant was therefore querying why Wyeth was continuing its audit programme *per se*, rather than focusing on the continued use of the FBI component that had been ruled in breach. The continuing GastroCare audit programme did not breach the undertaking given in Case AUTH/1561/3/04.

Wyeth submitted that it had taken considerable steps to review and amend materials and processes following the original complaint (Case AUTH/1561/3/04). As soon as Wyeth was aware of the present case appropriate action was taken to again review items in use to ensure that none of them could be in breach of the undertaking given in Case AUTH/1561/3/04. This review showed that the letter in question was the one item that had been missed. Wyeth submitted that as an additional step to avoid similar cases in the future, it had reviewed the interaction of various departments involved in the development and approval of such material to ensure central coordination of all issues.

Wyeth submitted that whilst it had accepted that high standards were not maintained in this case, it appealed the ruling of a breach of Clause 2.

COMMENTS FROM THE COMPLAINANT

The complainant noted that Wyeth was not challenging the fact that it was in breach of the Panel's ruling in Case AUTH/1561/3/04, but disagreed that

this had brought discredit upon, and reduced confidence in, the pharmaceutical industry. The complainant stated that he was happy for the Appeal Board to make a judgement on this case given its broader experience of the breaches that had merited this ruling in the past.

The complainant stated, in response to Wyeth's assertion that he was complaining about the audit programme *per se*, that whilst he had been misinformed by the BMJ news item it was the specific offer in the letter to switch lansoprazole capsules to Zoton FasTabs in GP practices which was the cause for his complaint. The complainant was concerned that this offer would result in recipients specifically requesting such a switch. When the complainant spoke to the Wyeth contact mentioned in the letter, they had stated that Wyeth would be able to support this, although they also mentioned the broader GastroCare programme. The complainant submitted that he was therefore not confident that if specifically requested to carry out the switch as a result of the letter, Wyeth would have abstained from doing so.

APPEAL BOARD RULING

The Appeal Board noted that the original letter was developed and prepared in March 2004. Wyeth had provided its undertaking and assurance in Case AUTH/1561/3/04 on 7 June 2004. The letter at issue, an amended form of the March letter, was produced in August 2004. The Appeal Board noted that the originator of the August letter had not been briefed on the outcome of Case AUTH/1561/3/04, or subsequent cases which concerned an alleged breach of the undertaking given in Case AUTH/1561/3/04 concerning Wyeth's switch programmes (Cases AUTH/1606/7/04, AUTH/1617/8/04, AUTH/1629/9/04 and AUTH/1655/11/04). The Appeal Board considered that this was unacceptable. It noted, with concern, that the letter had been signed off by a signatory familiar with Case AUTH/1561/3/04 and the subsequent cases which concerned the alleged breach of undertaking. Overall, the Appeal Board considered that Wyeth had brought discredit upon and reduced confidence in the Pharmaceutical Industry and so it upheld the Panel's ruling of a breach of Clause 2. The appeal on this point was unsuccessful.

COMMENTS FROM WYETH IN RELATION TO REPORT FROM THE PANEL

Before the Wyeth representatives commented on the report they were informed that the Appeal Board had ruled a breach of Clause 2 of the Code.

The Wyeth representatives stated that Code compliance was taken seriously by Wyeth and that it had taken steps to address the gap that contributed to the error being made. The representatives confirmed that the subsequent cases involving an alleged breach of undertaking had not triggered further analysis. The service at issue was no longer available; it had been replaced by a revised service. The Wyeth representatives stated that after the appeal in Case AUTH/1652/11/04 it had, on 3 March, stopped offering the revised service. This case was subject to a report from the Appeal Board to the ABPI Board of Management.

APPEAL BOARD CONSIDERATION OF THE REPORT

The Appeal Board noted that following Case AUTH/1561/3/04 there had subsequently been a number of complaints about the revised switch service. In responding to those complaints which concerned an alleged breach of the undertaking given in Case AUTH/1561/3/04, namely Cases AUTH/1606/7/04, AUTH/1617/8/04, AUTH/1629/9/04 and AUTH/1655/11/04, Wyeth had stated on each occasion that it had fully complied with the undertaking given. This submission was incorrect. After Case AUTH/1606/7/04, successive allegations of a breach of the undertaking in Case AUTH/1561/3/04 had not triggered further reviews of materials. As a result of the present case, Case AUTH/1659/11/04, it was apparent that Wyeth had not withdrawn all of the material at issue. The Appeal Board decided that, within the next month, Wyeth should be required to undergo a compulsory audit of its procedures relating to the Code as set out in Paragraph 10.4 of the Constitution and Procedure. Following receipt of the audit report the Appeal Board would then consider whether further action was necessary.

FURTHER CONSIDERATION BY THE APPEAL BOARD

The Appeal Board received the audit report. The Director reminded the Appeal Board that it had reported Wyeth to the ABPI Board of Management in relation to Case AUTH/1652/11/04. The ABPI Board of Management had decided that Wyeth should undergo an audit.

The Appeal Board decided that further action in Case AUTH/1659/11/04 was needed. It requested sight of the report for the audit required by the ABPI Board of Management in Case AUTH/1652/11/04. The Director pointed out that a decision would have to be made as to whether the Appeal Board could see an ABPI Board of Management audit report. The Appeal Board decided to defer consideration until that had been established. Nonetheless it decided that Wyeth should be re-audited in about nine months' time.

Complaint received **26 November 2004**

Case completed **22 June 2005**

CASE AUTH/1689/3/05

SERVIER/DIRECTOR v GLAXOSMITHKLINE

Breach of undertaking

Servier alleged that an Avandamet (rosiglitazone/metformin) leavepiece issued by GlaxoSmithKline was in breach of the undertaking given in Case AUTH/1620/7/04. The complaint was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with advice previously given by the Appeal Board.

In Case AUTH/1620/7/04 an Avandamet leavepiece was ruled in breach of the Code because it implied superiority of Avandamet over sulphonylureas in terms of glycaemic control over time. Servier considered that data presented in the leavepiece now at issue invited a similarly misleading comparison of Avandamet and sulphonylureas.

The Panel noted that Case AUTH/1620/7/04 concerned, *inter alia*, the presentation of data on a page headed 'Avandamet maintains lasting glycaemic control' which featured a graph, referenced to Jariwala *et al* (2003) depicting the persistent lowering of HbA_{1c} over $2^1/_2$ years when rosiglitazone was added to metformin. 'Stamped' over the lower right-hand corner of the graph was the claim 'UKPDS Sulphonylureas glycaemic control starts to deteriorate after one year'. The Panel had considered that as presented, the page at issue implied a direct comparison of Avandamet and sulphonylureas in which, after 1 year's treatment with sulphonylureas, glycaemic control, as measured by the levels of HbA_{1c}, was inferior to that achieved with Avandamet and depicted in the graph. The Panel had noted that, although HbA_{1c} rose after one year's treatment with sulphonylureas, and in that sense glycaemic control began to deteriorate, in absolute terms HbA_{1c} was still lower after 6 years' of treatment with sulphonylureas than after $2^1/_2$ years of Avandamet (7.1% vs 7.5% respectively). In terms of nationally recognised HbA_{1c} targets both groups were controlled at the end of each study. The Panel had disagreed with GlaxoSmithKline's submission that 'control' would be interpreted in a wide sense with no reference to a specific HbA_{1c} target. The Panel had also noted that there were significant differences between the patient groups included in Jariwala *et al* and the UKPDS. The patients in Jariwala *et al* were older than those in the UKPDS (57 vs 53) and had had diabetes for longer (7 years vs newly diagnosed). Baseline levels of HbA_{1c} were also higher in Jariwala *et al* (8.5% vs 6.9%). The Panel did not consider that the two groups of patients were comparable. The Panel considered that the presentation of the data was misleading and a breach of the Code was ruled.

Upon appeal by GlaxoSmithKline, the Appeal Board considered that 'sustained improvement in glycaemic control' as stated in the Avandamet SPC referred to a directional move. The claim in the leavepiece, however, referred to maintenance of lasting glycaemic control which the Appeal Board considered implied achievement and maintenance of targets. The Appeal Board upheld the Panel's ruling of a breach of the Code.

The Panel noted that the page at issue in the present case, Case AUTH/1689/3/05, was headed 'Avandamet delays disease progression' beneath which a graph depicted the change in HbA_{1c} over time when rosiglitazone was added to metformin. The graph was almost identical to that considered previously. Beneath a bold purple line the claim 'Sustained improvement in blood glucose' appeared above a box which contained two bullet points: 'In studies with a maximal duration of three years, Avandamet produced a sustained improvement in glycaemic control' referenced to the Avandamet SPC and 'In long-term studies with sulphonylureas, glucose levels begin to deteriorate at 3-12 months' referenced to UKPDS (1995), Birkeland *et al* (1994), Wolffenbuttel *et al* (1999), Drouin *et al* (2000).

The Panel noted that whilst there were differences between the material in question and that considered in Case AUTH/1620/7/04, the issue was whether these differences were such that the material was caught by the undertaking previously given.

The Panel did not accept GlaxoSmithKline's submission that the page was divided into two separate sections. The Panel considered that such a distinction was artificial; all the data on the page related to elements of glycaemic control. The bullet point 'In long-term studies with sulphonylureas, glucose levels begin to deteriorate at 3-12 months' was an integral part of a page which presented data from Jariwala *et al* showing the persistent lowering of HbA_{1c} over $2^1/_2$ years when rosiglitazone was added to metformin and referred to Avandamet delaying disease progression and producing a sustained improvement in both blood glucose control and glycaemic control. The Panel considered that overall the page invited the reader to, *inter alia*, unfavourably compare the deterioration of glucose levels with sulphonylureas at 3-12 months with Avandia's sustained improvement of glycaemic control over 3 years and persistent lowering of HbA_{1c} over $2^1/_2$ years. The Panel again noted that in UKPDS HbA_{1c} was still lower in absolute terms after 6 years' treatment with sulphonylureas than after $2^1/_2$ years' of Avandamet.

The Panel considered that whilst the revised material reflected some aspects of the ruling in Case AUTH/1620/7/04 the comparison of the deterioration in blood glucose levels with sulphonylureas at 3-12 months in long-term studies with Avandamet's long-term improvement in glycaemic control was closely similar to that in Case AUTH/1620/7/04 and thus failed to comply with the undertaking given in that case. The Panel considered that the comparison in the leavepiece in question constituted a breach of undertaking as alleged. High standards had not been maintained. Breaches of the Code were ruled.

An undertaking was an important document. The Panel considered that the revised material exacerbated the unfair nature of the original

comparison in Case AUTH/1620/7/04, reference was now made to deterioration of glucose levels at, *inter alia*, 3 months rather than one year as in the original comparison. The Panel considered that the failure to comply with the undertaking reduced confidence in and brought discredit upon the pharmaceutical industry; a breach of Clause 2 was ruled, which on appeal by GlaxoSmithKline was upheld.

The Panel considered that the failure to comply with the undertaking together with the exacerbation of the unfair nature of the original comparison warranted reporting the company to the Appeal Board for it to consider the matter in accordance with Paragraph 8.1 of the Constitution and Procedure.

The Appeal Board considered that there had been a clear breach of an undertaking and noted the exacerbation of the unfair nature of the original comparison. The Appeal Board also noted GlaxoSmithKline's previous history of breaches of the Code in the same therapeutic area and considered that these might be due to a cultural failure. The Appeal Board's extreme concern led it to report GlaxoSmithKline to the ABPI Board of Management in accordance with Paragraph 12.2 of the Constitution and Procedure, with the recommendation that the company should be publicly reprimanded.

The ABPI Board considered that undertakings were important documents; compliance with them was important for effective self regulation. The ABPI Board noted that there had been a clear breach of undertaking and that GlaxoSmithKline's appeal of a Clause 2 breach had been unsuccessful. The ABPI Board considered that this was an extremely serious matter which warranted the imposition of a public reprimand.

COMPLAINT

Servier noted that in Case AUTH/1620/7/04 an Avandamet leavepiece was ruled in breach of the Code because it implied superiority of Avandamet over sulphonylureas in terms of glycaemic control over time. In the leavepiece now at issue Servier considered that the data as presented on page 3 invited a comparison in relation to glycaemic control between Avandamet and sulphonylureas. In Case AUTH/1620/7/04, the Panel had considered that presenting the data in this way was misleading for two reasons. Firstly because although HbA_{1c} rose after one year's treatment with sulphonylureas, and in that sense glycaemic control began to deteriorate, in absolute terms HbA_{1c} was still lower after 6 years of treatment with sulphonylureas than after $2^1/_2$ years of Avandamet treatment (7.1% vs 7.5% respectively). And secondly, because there were significant differences between the Avandamet (Jariwala *et al* 2003) and sulphonylureas (UK Prospective Diabetes Study (UKPDS)) patient groups.

Servier alleged a breach of undertaking.

The complaint was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with advice previously given by the Appeal Board.

The Authority asked GlaxoSmithKline to respond in relation to Clauses 2, 9.1 and 22 of the Code.

RESPONSE

GlaxoSmithKline vigorously refuted Servier's allegation. The company had given careful consideration to the comments made by the Panel and the Appeal Board in the previous case when it had amended the glycaemic control page in the leavepiece now at issue. The page was now clearly divided into two separate sections. These sections were separated by a thick horizontal line, and each section had its own heading. The two headings were of equal typographical weight. Each section was evidently intended to be considered on its own individual merits.

GlaxoSmithKline noted that the headlined claim in the upper section was referenced to four sources providing evidence for long-term reductions in glycaemia with rosiglitazone and Avandamet; and for delay in the need for insulin injections in Avandamet-treated patients. One of these sources was Jariwala *et al*; and the graph relating to this study was reproduced, as in the original leavepiece. However, unlike the original, no comparison was drawn between the Jariwala *et al* graph and the long-term glycaemic effects of sulphonylureas. Indeed, sulphonylureas were not mentioned at all in the upper section of the page.

GlaxoSmithKline noted that the lower section of the page headed 'Sustained improvement in blood glucose' incorporated two claims enclosed within a separate box. The first claim concerned Avandamet, and took full account of the Appeal Board's views on the use of the phrase 'glycaemic control'. The claim had been amended to reflect the exact wording of the statement in the pharmacodynamics section of the Avandamet summary of product characteristics (SPC), and was referenced solely to the SPC itself.

The second claim related to the long-term effects of sulphonylureas. Contrary to the implication by Servier, this statement was no longer referenced only to the UKPDS, but four separate studies – representing all of the well-controlled studies on long-term sulphonylurea effects that GlaxoSmithKline had identified in the literature. Furthermore, the wording had been amended from an emphasis on glycaemic control to one on deterioration of glucose levels – again, in compliance with the Appeal Board's views.

In summary, GlaxoSmithKline submitted the sulphonylurea statement was balanced, accurate, and reflected the totality of the available literature; and was contrasted with a claim for Avandamet based on, and reproducing the wording of, a statement contained in the Avandamet SPC. The sulphonylurea statement was no longer compared, directly or indirectly, with the data from Jariwala *et al*. The latter was only used to exemplify a completely separate claim, itself sustained by three references additional to Jariwala *et al*. Finally, the wording on the page had been amended throughout to reflect the Appeal Board's views on the use of the phrase 'glycaemic control'.

GlaxoSmithKline submitted therefore, that it had in all respects complied with the undertaking.

PANEL RULING

The Panel considered that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in future. It was important for the reputation of the industry that companies complied with undertakings.

The Panel noted that the previous case, Case AUTH/1620/7/04, concerned, *inter alia*, the presentation of data on a page headed 'Avandamet maintains lasting glycaemic control' which featured a graph, referenced to Jariwala *et al* depicting the persistent lowering of HbA_{1c} over $2^1/_2$ years when rosiglitazone was added to metformin. 'Stamped' over the lower right-hand corner of the graph was the claim 'UKPDS Sulphonylureas glycaemic control starts to deteriorate after one year'.

Case AUTH/1620/7/04

The Panel noted that the claim 'UKPDS sulphonylurea: glycaemic control starts to deteriorate after 1 year' was 'stamped' across the bottom right-hand corner of the graph depicting the results of Jariwala *et al*. The Panel considered that, as presented, the claim implied a direct comparison of Avandamet and sulphonylureas in which, after 1year's treatment with sulphonylureas, glycaemic control, as measured by the levels of HbA_{1c}, was inferior to that achieved with Avandamet and depicted in the graph. The Panel noted that, although HbA_{1c} rose after one year's treatment with sulphonylureas, and in that sense glycaemic control began to deteriorate, in absolute terms HbA_{1c} was still lower after 6 years' of treatment with sulphonylureas than after $2^1/_2$ years of Avandamet treatment (7.1% vs 7.5% respectively). In terms of HbA_{1c} targets set by the GMS contract and/or NICE both groups were controlled at the end of each study. The Panel disagreed with GlaxoSmithKline's submission that 'control' would be interpreted in a wide sense with no reference to a specific HbA_{1c} target. The graph, over which the claim in question was 'stamped', depicted specific HbA_{1c} levels and the claim would thus be read in the context of these levels.

The Panel noted that there were significant differences between the patient groups included in Jariwala *et al* and the UKPDS. The patients in Jariwala *et al* were older than those in the UKPDS (57 vs 53) and had had diabetes for longer (7 years vs newly diagnosed). Baseline levels of HbA_{1c} were also higher in Jariwala *et al* (8.5% vs 6.9%). The Panel did not consider that the two groups of patients were comparable.

The Panel considered that, as presented, page 2 of the leavepiece was misleading as alleged. A breach of the Code was ruled.

Upon appeal by GlaxoSmithKline, the Appeal Board noted that Section 5.1, Pharmacodynamic properties of the Avandamet SPC stated that 'In studies with a maximal duration of three years, rosiglitazone given once or twice daily in combination with metformin produced a sustained improvement in glycaemic control …'. The Appeal Board considered that 'sustained improvement in glycaemic control' referred to a directional move. The claim in the leavepiece, however, referred to maintenance of lasting glycaemic control which the Appeal Board considered implied achievement and maintenance of targets.

The Appeal Board considered that, as presented, page 2 of the leavepiece was misleading as alleged. The Appeal Board upheld the Panel's ruling of a breach of the Code.

Case AUTH/1689/3/05

The Panel noted that the page at issue in Case AUTH/1689/3/05 was headed 'Avandamet delays disease progression' beneath which a graph depicted the change in HbA_{1c} over time when rosiglitazone was added to metformin. The graph was identical to that considered previously save the Y axis was annotated in months rather than years. Beneath a bold purple line the claim 'Sustained improvement in blood glucose' appeared above a box which contained two bullet points: 'In studies with a maximal duration of three years, Avandamet produced a sustained improvement in glycaemic control' referenced to the Avandamet SPC and 'In long-term studies with sulphonylureas, glucose levels begin to deteriorate at 3-12 months' referenced to UKPDS (1995), Birkeland *et al* (1994), Wolffenbuttel *et al* (1999), Drouin *et al* (2000).

The Panel noted that whilst there were differences between the material in question and that considered in Case AUTH/1620/7/04, the issue was whether these differences were such that the material was caught by the undertaking previously given.

The Panel did not accept GlaxoSmithKline's submission that the page was divided into two separate sections. The Panel considered that such a distinction was artificial; all the data on the page related to elements of glycaemic control, indeed, GlaxoSmithKline referred to it as 'the glycaemic control page'. The bullet point 'In long-term studies with sulphonylureas, glucose levels begin to deteriorate at 3-12 months' was an integral part of a page which presented data from Jariwala *et al* showing the persistent lowering of HbA_{1c} over $2^1/_2$ years when rosiglitazone was added to metformin and referred to Avandamet delaying disease progression and producing a sustained improvement in both blood glucose control and glycaemic control. The Panel considered that the overall effect of the page was such that it invited the reader to, *inter alia*, unfavourably compare the deterioration of glucose levels with sulphonylureas at 3-12 months with Avandia's sustained improvement of glycaemic control over 3 years and persistent lowering of HbA_{1c} over $2^1/_2$ years. The Panel noted, however, that in UKPDS although HbA_{1c} rose after one year's treatment with sulphonylureas and thus glycaemic control began to deteriorate, in absolute terms HbA_{1c} was still lower after 6 years' treatment with sulphonylureas than after $2^1/_2$ years' of Avandamet treatment.

The Panel considered that whilst the revised material reflected some aspects of the ruling in Case

AUTH/1620/7/04 the comparison of the deterioration in blood glucose levels with sulphonylureas at 3-12 months in long-term studies with Avandamet's long-term improvement in glycaemic control was closely similar to that in Case AUTH/1620/7/04 and thus failed to comply with the undertaking given in that case. The Panel considered that the comparison in the leavepiece in question constituted a breach of undertaking as alleged; a breach of Clause 22 was ruled. High standards had not been maintained; a breach of Clause 9.1 was ruled.

The Panel considered that an undertaking was an important document. The Panel considered that the revised material exacerbated the unfair nature of the original comparison in Case AUTH/1620/7/04, reference was now made to deterioration of glucose levels at, *inter alia*, 3 months rather than one year as in the original comparison which further exaggerated the misleading impression about the longer term differences in HbA_{1c} levels between the products. The Panel considered that the failure to comply with the undertaking reduced confidence in and brought discredit upon the pharmaceutical industry; a breach of Clause 2 was ruled.

The Panel considered that the failure to comply with the undertaking together with the exacerbation of the unfair nature of the original comparison warranted reporting the company to the Appeal Board for it to consider the matter in accordance with Paragraph 8.1 of the Constitution and Procedure.

APPEAL BY GLAXOSMITHKLINE

GlaxoSmithKline submitted that having reviewed the ruling in Case AUTH/1620/8/04 there were two significant issues. The first issue surrounded the wording relating to 'diabetic control' – all instances of which were subsequently changed in the revised piece to be in accordance with the Avandamet SPC by using quotations from the SPC in all instances. The second issue on which the original materials were found to be in breach lay in the explicit comparison between the results of Jariwala *et al* and those of the UKPDS. The Panel and Appeal Board considered that the methodologies of the two studies were too dissimilar to allow direct comparison.

GlaxoSmithKline stated that the bottom half of the revised leavepiece comprised of two statements. The first, which related to the sustained improvement in blood glucose seen with Avandamet (in studies of up to three years' duration), was from the Avandamet SPC and thus required no additional reference. The second related to the long-term effects of sulphonylureas on diabetic control and was referenced to four studies (including the UKPDS). All of these studies indicated that the initial improvements in glucose seen with sulphonylureas were not maintained over the longer term and that glucose levels began to rise again within three to twelve months. These four studies represented, at the time, practically the only available data on the long-term efficacy of sulphonylureas (further evidence supporting the statement had since been published). The overwhelming balance of available evidence indicated that blood glucose control with sulphonylureas was not sustained over the longer term. Broadening the sulphonylurea references therefore strengthened and further validated the sulphonylurea statement without drawing a comparison to Jariwala *et al*. The statement 'In long-term studies with sulphonylureas, glucose levels begin to deteriorate at 3-12 months' was a fair representation of all the evidence available for long-term data with sulphonylureas and was substantiable, based on the extensive data referenced. There was no intention of aggravating the original breach.

GlaxoSmithKline submitted that the Avandamet SPC contained an unambiguous statement that sustained improvements in glycaemic control of up to three years' duration were obtained with Avandamet. Therefore, the comparison drawn was entirely valid on the available evidence; if the information on the page in question was restricted to these two statements, no issue could possibly have arisen as to any breach of the Code.

GlaxoSmithKline submitted that the clear separation of the graph from Jariwala *et al* at the top of the page from the two statements at the bottom of the page, by using boxing off and using a separate heading and a thick horizontal bar between the two sections, rendered the material compliant with its previous undertaking. At most, the graph might be seen as illustrative of the Avandamet SPC statement. In the revised leavepiece, no comparison was drawn between Jariwala *et al* and the UKPDS, or indeed any specific sulphonylurea study. As such, the page as a whole respected the previous undertaking.

GlaxoSmithKline noted that its view clearly differed from that of the Panel on the impression that might be given by these materials; it respected that judgement, and had not appealed the breaches of Clauses 22 and 9.1. GlaxoSmithKline took decisions of the Panel and Appeal Board, and its undertakings as a result of such decisions, extremely seriously. Given the background outlined above, GlaxoSmithKline hoped that it would be evident that the revision to the original leavepiece was made in good faith, was extensive and significant, and clearly reflected an intention to comply with the undertaking given. GlaxoSmithKline did not consider that its actions in this case could be construed as reducing confidence in, or bringing discredit upon, the industry. The company denied a breach of Clause 2.

COMMENTS FROM SERVIER

Servier agreed with the Panel that an undertaking was an important document and that failure to comply with the undertaking reduced confidence in and brought discredit upon the pharmaceutical industry and therefore warranted a ruling of a breach of Clause 2.

Servier noted that 'The Panel considered that the revised material exacerbated the unfair nature of the original comparison in Case AUTH/1620/7/04, reference was now made to deterioration of glucose levels at, *inter alia*, 3 months rather than one year as in the original comparison which further exaggerated the misleading impression about the longer term differences in HbA_{1c} levels between the products'.

Servier noted that the original material which contained the misleading and unfair claims was prepared in May 2004 and it had first complained to the Authority about these claims in August 2004 after intercompany dialogue with GlaxoSmithKline had failed to reach a satisfactory resolution. The claims were ruled in breach after appeal in December 2004. The 'revised' material, which was the subject of the present complaint was prepared in December 2004 and was ruled in breach in May 2005. These misleading and unfair claims had therefore been used by GlaxoSmithKline for over one year.

Servier noted that since Avandia/Avandamet had gained marketing authorizations (July 2000 and October 2003), the products' promotional material had been the subject of complaint in eleven separate cases and 47 breaches had been ruled. These included one breach of Clause 2, two breaches of undertaking, two reports to the ABPI Board of Management and a public reprimand.

Servier found it difficult to reconcile this record of repeated and persistent use of promotional material which did not comply with either the Code or with undertakings with GlaxoSmithKline's defence in this case. Servier agreed with the Panel's ruling of a breach of Clause 2.

APPEAL BOARD RULING

The Appeal Board noted that the leavepiece in Case AUTH/1620/7/04 had been ruled in breach of the Code because by directly comparing Jarawala *et al* with the UKPDS it gave the misleading impression that Avandamet achieved glycaemic control and maintained it, whereas sulphonylureas did not. The Appeal Board noted that although the leavepiece now at issue in Case AUTH/1689/3/05 was different, the overall message was the same. GlaxoSmithKline had accepted breaches of Clauses 9.1 and 22 of the Code. The Appeal Board did not accept that the page in question was divided into two halves such that the data presented in each would be read separately. The Appeal Board also noted that although the data set for sulphonylureas had been expanded the UKPDS still contributed by far the greatest proportion of patients.

The Appeal Board considered that, whereas in the original leavepiece it was implied that glycaemic control deteriorated with sulphonylureas after one year the leavepiece now at issue implied that such deterioration occurred as early as three months. In absolute terms, however, sulphonylureas produced a lower HbA_{1c} than Avandamet.

The Appeal Board considered that the revised leavepiece had repeated and exacerbated the unfair comparison in Case AUTH/1620/7/04 and upheld the Panel's ruling of a breach of Clause 2. The appeal on this point was unsuccessful.

REPORT FROM THE PANEL TO THE APPEAL BOARD

The Appeal Board considered that there had been a clear breach of an undertaking and noted the exacerbation of the unfair nature of the original comparison. The Appeal Board also noted GlaxoSmithKline's previous history of breaches of the Code in the same therapeutic area and considered that these may be due to a cultural failure. The Appeal Board was extremely concerned such that it decided to report GlaxoSmithKline to the ABPI Board of Management in accordance with Paragraph 12.2 of the Constitution and Procedure, with the recommendation that the company should be publicly reprimanded.

ABPI BOARD OF MANAGEMENT CONSIDERATION

The ABPI Board considered that an undertaking was an important document. Compliance with undertakings was important for effective self regulation. The ABPI Board noted that there had been a clear breach of undertaking and noted that the GlaxoSmithKline appeal of a Clause 2 breach had been unsuccessful. The ABPI Board considered that this was an extremely serious matter which warranted the imposition of a public reprimand.

Complaint received	**10 March 2005**
PMCPA proceedings completed	**11 July 2005**
ABPI Board proceedings completed	**19 October 2005**

CASE AUTH/1700/4/05

PARAGRAPH 17/DIRECTOR v WYETH

Switch programme

During its consideration of Case AUTH/1652/11/04 which concerned the role of the representative in relation to a switch programme, the GastroCare Service run by Wyeth, the Code of Practice Appeal Board decided that certain matters not the subject of the complaint be taken up with Wyeth in accordance with Paragraph 17.1 of the Constitution and Procedure.

The Appeal Board had been concerned about the overall arrangements for the switch programme but it had had no complaint before it in this regard. The Appeal Board noted that Wyeth's submission at the appeal hearing that 'the Panel did not find services offered unacceptable' was incorrect. The Panel had not considered the acceptability of the overall arrangements in relation to the Code. Case AUTH/1652/11/04 had concerned the role of the representative in relation to the revised service. The Appeal Board queried whether the switch programme was a *bona fide* medical and educational good or service which enhanced patient care or benefited the NHS as stated in the Code. The Appeal Board decided that its concerns should be taken up as a separate complaint with Wyeth.

The Panel noted that the GastroCare Service at issue was that implemented during July 2004. Wyeth had suspended the offer of its GastroCare Service in March 2005.

The Panel's role in the present case was to consider whether the GastroCare Service was a *bona fide* medical and educational good and service.

The medication review spreadsheet on which the prescribing decision (new medicine and dose) was indicated stated that a GastroCare service was available to review any oral proton pump inhibitor (PPI) and dose at the request of the practice and listed all strengths and formulations of esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole.

The services were only offered by the representative once a prescribing decision (new medicine and dose) had been made. The Panel was concerned that it appeared that the arrangements were such that the health professional was required to decide on the new medication without encouragement to consider relevant factors such as NICE guidance, cost of various medicines and local prescribing policies etc. The Panel accepted that the medication review sheet did not commit health professionals.

The Panel noted that the GastroCare service comprised two distinct services. If the doctor only wished to change formulation then the GPSSI (GP Systems Specialist Implementation) service would be offered. If the doctor wished to change patients from one PPI to another or effect any dose changes then the GastroCare Audit and Review service would be offered.

The GPSSI service would be explained to the doctor using the GPSSI Pack. Further details appeared in the representatives' briefing material, Action Plan: GastroCare Service offerings. Each partner in a practice had to sign the booking/consent form for the GPSS who would then search the computerized patient list to identify relevant patients as per the medication review spreadsheet. The GPs would then review and authorize these changes in relation to each patient as set out on the medication review spreadsheet using the practice formulary spreadsheet. The GPSS would then implement these changes.

The GPSSI Pack did not describe the enhancement to patient care or benefit to the NHS of that service. Reference was made to cost savings and the opportunity to benefit from a more convenient product formulation such as an oro-dispersible formulation without any change to the therapeutic qualities of the product.

If the GastroCare Audit and Review option was offered the Action Plan: GastroCare Service Offerings stated that the representative would explain the service using the GastroCare detail aid which set out two implementation methods: either by using a nurse, or by using a GPSS and a nurse.

The booklet, Upper GI Therapy and Review – Wyeth GastroCare Nurses, was left with GPs who had chosen the nurse only audit and provided further details. A treatment management plan would be completed by the nurse with the practice. The treatment management plan consisted of five columns headed 'Patient Type', 'Change From', 'Stepped Care Policy', 'Change to' and 'Presentation eg capsule, tablet, suspension'.

A computer printout was then generated of all patients who had had more than three prescriptions in twelve months from which the GP could identify and exclude patients from the audit. Sixteen suggested exclusion criteria were given. The nurse would then set up an electronic Gastro Register which featured patients' personal details, medication, diagnosis, symptom control etc. The audit flow chart then set out three options; firstly the nurse would identify patients suitable for change of medication by letter, as per the treatment management plan, although the Panel noted that no such option was provided for in the specimen treatment management plan; secondly the nurse would identify patients requiring further consultation and thirdly identify those to be reviewed via clinic. Patients suitable for medication change were agreed with the GP and the changes implemented.

The audit undertaken by the nurse and GPSS was similar and set out in Upper GI Therapy and Review which was left with the practice. The initial computer search was undertaken by the GPSS who would identify all patients on continuous therapy from which the GPSS would produce a detailed patient profile spreadsheet, the Gastro Register. Reference was made to a list of suggested exclusion criteria identical to that in the nurse only audit. It

was unclear how these criteria could be agreed by the GP at this stage as according to the audit flow chart no meeting had yet taken place with the GP to agree the parameters of the initial search. The matter was not dealt with on the booking and consent form. It was also unclear why the initial search criteria were different to the nurse only audit. A nurse would then attend and complete the treatment management plan with the GP and finalise the Gastro Register in accordance with it. Actions would be agreed with and authorized by the GP. The GPSS would then attend and complete changes to the patients' medication on the computer.

The GastroCare Audit and Review detail aid set out the reasons why an upper GI audit should be performed. These included the number of patients who could potentially benefit; GI medicines accounted for a substantial part of time and money spent on primary care; repeat prescriptions might lead to inappropriate medicines management as patients needs changed; all primary care organisations should review the use of PPIs according to NICE guidance on the use of PPIs in the treatment of dyspepsia; and NHS performance indicators, as prescribing ulcer healing drugs was one of ten indicators by which the Department of Health assessed the performance of health authorities and trusts. The detail aid explained that the audit and review would enable practices to achieve upper GI audit with minimal impact on workload; meet incentives linked to PPI prescribing; improve patient education; achieve consistency of practice prescribing and patient care; promote best practice prescribing in accordance with NICE; meet the needs of clinical governance; free up practice time; contribute to GP appraisals and provide a comprehensive review report.

The GastroCare Audit and Review booklets each left with the practice raised points similar to those in the detail aid. More emphasis was given to the NICE guidance on the use of PPIs in the treatment of dyspepsia which was described as being of particular importance. It was noted that NICE concluded that all doctors should review their use of PPIs in dyspepsia (or gastrointestinal oesophageal reflux disease (GORD)) meaning that any audit in this area would contribute to achieving national goals for prescribing. Further the availability of such guidance made it relatively straightforward to set standards for achieving best practice.

The Panel noted various sections of the NICE guidance including Section 1.7 which stated that the least expensive appropriate PPI should be used.

The Panel considered that this was a difficult area. It decided to consider the GPSSI service and the GastroCare Audit and Review separately. The way the services were offered ie in the context of a promotional Zoton FasTab call was not irrelevant, although the Panel noted that the role of the representative was outside the scope of the complaint.

The Panel considered that it was difficult to see how the GPSSI service would enhance patient care or benefit the NHS. The GPSSI service was offered after the GP had made the decision to switch formulation within the context of a promotional Zoton FasTab call. Whilst the medication changes were authorized by the practice it was difficult to see at what point any consideration was given to whether a change of formulation would enhance patient care or benefit the NHS. Such enhancement or benefit might, perchance, be a consequence of such a change, but the consideration of such issues did not appear to be an integral part of the service. In the Panel's view consideration of benefit to the NHS or the enhancement of patient care must be an integral and demonstrable part of the service. Whilst such factors might well be borne in mind by the prescriber such consideration did not arise as a consequence of any element of the service. This was particularly so given Wyeth's submission that the initial prescribing decision was made prior to the offer of the service. The Panel decided that the GPSSI service was not a medical and educational good or service within the meaning of the Code and thus a breach of the Code was ruled. High standards had not been maintained and a further breach of the Code was ruled. Nonetheless the Panel did not consider that the GPSSI service reduced confidence in or brought discredit upon the pharmaceutical industry so no breach of Clause 2 was ruled.

The Panel considered that there were differences between the GastroCare Audit and Review and the GPSSI service. Consideration of some factors set out in the NICE guidance were an integral part of the GastroCare Audit and Review. The GastroCare register would continue to benefit the practice after the audit. The Panel was concerned, however, that there was no reference to prescribing the least expensive appropriate PPI. This was a significant omission given the weight attached to the NICE guidance. The Panel was also concerned that a prescribing decision had to be made prior to the offer of the service. However, the Panel considered that this was balanced by the completion of the treatment management plan. The Panel considered that, on balance, the GastroCare Audit and Review service would enhance patient care or benefit the NHS and no breach of the Code was ruled.

COMPLAINT

During its consideration of Case AUTH/1652/11/04 which concerned the role of the representative in relation to a switch programme, the GastroCare Service run by Wyeth Pharmaceuticals, the Code of Practice Appeal Board decided that certain matters, not the subject of the complaint be taken up with Wyeth in accordance with Paragraph 17.1 of the Constitution and Procedure.

Case AUTH/1652/11/04

During its consideration of the appeal in this case the Appeal Board was concerned about the overall arrangements for the switch programme in relation to the requirements of Clauses 2, 9.1 and 18.1 of the Code. The Appeal Board noted that it had no complaint before it in this regard.

The Appeal Board noted Wyeth's submission at the appeal hearing that 'the Panel did not find services offered unacceptable'. This was incorrect. The Appeal Board noted that the Panel had not considered the acceptability of the overall arrangements in relation to Clause 18.1. Case AUTH/1652/11/04 had concerned the role of the representative in relation to the revised service.

The Appeal Board queried whether the switch programme was a *bona fide* medical and educational good or service which enhanced patient care or benefited the NHS as stated in the supplementary information to Clause 18.1 Provision of Medical and Educational Goods and Services.

The Appeal Board decided that its concerns should be taken up as a separate complaint with Wyeth. This was in accordance with Paragraph 17.1 of the Constitution and Procedure.

RESPONSE

Wyeth denied that the overall arrangements for the GastroCare Service were in breach of Clauses 2, 9.1 or 18.1 of the Code. As the arrangements for the implementation of the GastroCare Service, in particular the role of Wyeth's representatives, had already been addressed in Case AUTH/1652/11/04, it did not deal with these arrangements again.

The GastroCare Service offered by Wyeth was not product specific and could be offered and performed in respect of any relevant medicine (ie proprietary or generic) of the GP's choice in the appropriate therapeutic categories. Wyeth offered this service as a medical service to enhance patient care and benefit the NHS. The supplementary information to Clause 18.1 stated that this clause did not prevent the provision of such services provided that they were not done in such a way as to be an inducement to prescribe. Wyeth had considered the requirements of Clause 18.1 and its supplementary information and was satisfied that it had complied with the Code and that it could provide this valuable service to the NHS.

Wyeth provided copies of material which set out the details of the service at the time of the original complaint which gave rise to this request (July 2004).

1 The Wyeth GastroCare pack (outer folder ZZOT3586) used by representatives which included Medication Review Spreadsheet folder (ZZOT3587); GastroCare Audit and Review – The Case for PPI [proton pump inhibitor] Patient Management in Upper GI Disease (ZZOT3414); GP Systems Specialist Implementation Pack (ZZOT3588); and a Data Protection letter (ZZOT3572).

2 Upper GI Therapy Audit and Review – Wyeth GastroCare Nurses (ZZOT3415) – used by one of Wyeth's nurse teams.

3 Upper GI Therapy Audit and Review – Wyeth GastroCare Nurses (ZZOT3416) – used by the other Wyeth nurse teams.

Internal documents which detailed the arrangements for the two components of the then GastroCare Service and were given to Wyeth's representatives as part of the briefing and training on the service at the time were as follows: Action Plan: GastroCare Service Offerings (ZZOT3580); Action Plan Questions & Answers (ZZOT3603); GastroCare Process Flowchart (ZZOT3601); GastroCare Service Decision Tree (ZZOT3602); GastroCare GP Systems Specialist and Audit Review Service – Representative Briefing Document (ZZOT3581); Step-by step guide to the 'Telephone Scheduling Service' (ZZOT3624).

When a GP was interested in reviewing their or their practice's PPI prescribing the procedure as set out in the representatives' briefing document 'Action Plan: GastroCare Service Offerings' was used to offer the GastroCare Service as follows:

The GP was asked to indicate the PPIs (s)he wished to implement/review by completing and signing the Medication Review Spreadsheet. If the GP wished to change from prescribing one PPI to prescribing another, or wanted to implement a dose change, then a full audit and review was needed and an appointment would be made for a GastroCare Specialist to explain to the GP in detail the service to be provided (using the GastroCare Audit and Review – The Case for PPI Patient Management in Upper GI Disease material). If the GP accepted this service offering, they completed the GastroCare Nurse/Booking Consent Form and arrangements were then made for an external supplier to carry out the service at the practice. The relevant Upper GI Therapy Audit and Review booklet, which detailed the arrangements for the service, would be left with the practice.

If the GP only wanted to change prescribing from one formulation of a PPI to another formulation of the same PPI in a dose for dose switch (eg lansoprazole capsules 15 mg to lansoprazole oro-dispersible tablets 15mg, omeprazole tablets 20mg to omeprazole capsules 20mg), then the representative would offer the GP Systems Specialist Implementation (GPSSI) service, using the GPSSI Pack to show how the service would be carried out. If the GP accepted the service offering then (s)he completed the Practice Booking and Consent Form and the Wyeth representative arranged for an external supplier to carry out the service at the practice.

Wyeth considered that both elements of the then GastroCare Service, the GPSSI service and the GastroCare Audit and Review service enhanced patient care and benefited the NHS. The GP's identified prescribing preference dictated which service was discussed in detail and implemented. If a GP only wished to make a simple formulation change, a full audit and review was not necessary. However, if a GP was uncomfortable with the simple GPSSI service, the GastroCare Audit and Review service was an option.

The GPSSI service enabled GPs and practices to quickly and effectively change from one PPI or formulation to a therapeutically equivalent one, eg change from lansoprazole capsules to lansoprazole oro-dispersible tablets which would cost the practice and the NHS less. Due to the high prevalence of dyspepsia and the large number of patients being treated with PPIs, there would be significant cost

savings available. Patients also benefited from a more convenient formulation without any change to the therapeutic qualities of the product. The significant convenience benefit for the patient in this case was that lansoprazole oro-dispersible tablets could be taken without water enabling the patient to take them wherever they were. This might also help patients with compliance.

In relation to the GastroCare Audit and Review service, audit and review was an activity conducted extensively across the NHS both by the NHS itself and with the support of the pharmaceutical industry. Audit was a central component of clinical governance in primary and secondary care. In the case of this service, the benefits of the service were discussed in detail in the 'Why do an Upper GI Audit?' section at the beginning of ZZOT3414. Specifically, in the relevant National Institute for Clinical Excellence (NICE) guidance on the use of PPIs in the treatment of dyspepsia (July 2000), NICE concluded that all primary care organisations should review the use of PPIs in the treatment of dyspepsia in accordance with their guidance. Further, prescribing of ulcer healing medicines was one of only ten indicators by which the Department of Health assessed the performance of health authorities and trusts. Accordingly, the service was designed, *inter alia*, to help practices meet local and national goals on PPI prescribing, deliver improved patient education, achieve consistency across practice prescribing and patient care, promote best practice prescribing in accordance with the NICE guidance and meet the needs of clinical governance and the Commission for Healthcare Audit and Inspection (CHAI). Again, due to the high prevalence of dyspepsia, the outcome of audit and review would have an impact upon the care of a significant number of patients, including possibly reducing adverse events. There was also a clear benefit for the NHS in, for example, stopping inappropriate use of PPIs, switching from a healing dose to a lower (and cheaper) maintenance dose, switching from one PPI product or formulation to a therapeutically equivalent but cheaper one, and/or reducing the number of investigations performed such as endoscopy and/or inappropriate referrals to secondary care.

Of course, patients also benefited from best practice prescribing in accordance with the NICE guidance in that, for example, following treatment with an appropriate PPI healing dose, patients could be stepped down to the lowest possible dose that maintained and controlled symptoms. Audits could often highlight patients who might have been on medication for some years without any review.

Save for the initial introduction and offer of the service by a representative (a matter discussed in Case AUTH/1652/11/04), the representative was not involved in the provision of the GastroCare Service. Third party service providers, registered nurses in the case of the audit and review services, implemented the service itself.

Wyeth considered that the range of programmes offered as part of the GastroCare Service benefited patient care and the NHS, met the guidance given in the supplementary information to Clause 18.1 and consequently did not breach Clause 18.1. They were conducted to a high standard, and were well received by health professionals, and consequently Wyeth also refuted Clause 2 and 9.1 breaches. Indeed, Wyeth was happy to provide the Authority with customer letters confirming their endorsement and support of the GastroCare programme.

PANEL RULING

The Panel noted that the GastroCare Service at issue was that implemented during July 2004. [The Panel noted that during the Appeal Board's consideration of Case AUTH/1659/11/04 on 30 March Wyeth had stated that in light of the Appeal Board's consideration of Case AUTH/1652/11/04 it had suspended the offer of its GastroCare Service on 3 March 2005].

The Panel noted that the role of the representative in relation to the GastroCare Service had been the subject of previous complaints. The Panel's role in the present case was to consider whether the GastroCare Service was a *bona fide* medical and educational good and service within the meaning of the supplementary information to Clause 18.1 of the Code. The supplementary information to Clause 18.1 permitted the provision of medical and educational goods and services which enhanced patient care or benefited the NHS so long as they were not an inducement to prescribe, supply, administer, recommend or buy any medicine.

The medication review spreadsheet folder (ZZOT3587) which contained the medication review spreadsheet on which the prescribing decision (new medicine and dose) was indicated stated that a GastroCare service was available to review any oral PPI and dose at the request of the practice and listed all strengths and formulations of esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole.

The Panel noted that the services were only offered by the representative once a prescribing decision (new medicine and dose) had been made. It seemed odd to the Panel that a doctor would indicate a prescribing decision, in writing, other than in the context of the provision of a service in which (s)he was interested. Nonetheless, the Panel noted Wyeth's submission on this point. The Panel was also concerned that it appeared that the arrangements were such that the health professional was required to decide on the new medication without encouragement to consider relevant factors such as NICE guidance, cost of various medicines and local prescribing policies etc. The Panel accepted that the medication review sheet did not commit health professionals.

The Panel noted that the GastroCare service comprised two distinct services; if the doctor only wished to change formulation then the GPSSI service would be offered. If the doctor wished to change patients from one PPI to another or effect any dose change then the GastroCare Audit and Review would be offered.

The GPSSI service would be explained to the doctor using the GPSSI Pack (ZZOT3588). Further details appeared in the representatives' briefing material,

Action Plan: GastroCare Service offerings (ZZOT3580). Each partner in a practice had to sign the booking/consent form for the GPSS who would then search the computerized patient list to identify relevant patients as per the medication review spreadsheet. The GPs would then review and authorize these changes in relation to each patient as set out on the medication review spreadsheet using the practice formulary spreadsheet. The GPSS would then implement these changes.

The GPSSI Pack featured examples of patient letters; a flowchart stated these would be generated by the GPSS whilst the introduction to the letters stated that they could be written by the practice. The GPSSI Pack did not describe the enhancement to patient care or benefit to the NHS of that service. The Panel also noted Wyeth's submission that the GPSSI service was quick and effective. Reference was made to cost savings and the opportunity to benefit from a more convenient product formulation such as an oro-dispersible formulation without any change to the therapeutic qualities of the product.

If the GastroCare Audit and Review option was offered the Action Plan: GastroCare Service Offerings stated that the representative would explain the service using the GastroCare detail aid (ZZOT3414) which set out two implementation methods; either by using a nurse, or by using a GPSS and a nurse.

The booklet, Upper GI Therapy and Review – Wyeth GastroCare Nurses (ZZOT3416) was left with GPs who had chosen the nurse only audit and provided further details. A treatment management plan would be completed by the nurse with the practice. The treatment management plan consisted of five columns headed 'Patient Type', 'Change From', 'Stepped Care Policy', 'Change to' and 'Presentation eg capsule, tablet, suspension'. Five different 'patient types' were described including those well controlled on a higher dose and those well controlled on a maintenance dose. The 'Change From' column gave details of various medicines at various doses for each of the patient types. The 'Stepped Care Policy' column described an approach for each patient type such a 'eg Step down', 'eg Change of PPI'. The 'Change to' column included a space for the identification of a PPI of choice for each of the patient types plus a requirement to review certain changes at 4-8 weeks. The final column 'Presentation' was to be completed with for example capsule, tablet, suspension.

A computer printout was then generated of all patients who had had more than 3 prescriptions in 12 months from which the GP could identify and exclude patients from the audit. Sixteen suggested exclusion criteria were given – such as on a PPI for 8 weeks or awaiting endoscopy or GI-related hospital appointment. The nurse would then set up an electronic Gastro Register which featured patients' personal details, medication, diagnosis, symptom control etc. The audit flow chart then set out 3 options; firstly the nurse would identify patients suitable for change of medication by letter, as per the treatment management plan although the Panel noted that no such option was provided for in the specimen treatment management plan set out in ZZOT3416; secondly the nurse would identify patients requiring further consultation and thirdly identify those to be reviewed via clinic. Patients suitable for medication change were agreed with the GP and the changes implemented. Example letter templates were provided.

The audit undertaken by the nurse and GPSS was similar and set out in Upper GI Therapy and Review (ZZOT3415) which was left with the practice. The initial computer search was undertaken by the GPSS who would identify all patients on continuous therapy from which the GPSS would produce a detailed patient profile spreadsheet, the Gastro Register. Reference was made to a list of suggested exclusion criteria identical to that in the nurse only audit. It was unclear how these criteria could be agreed by the GP at this stage as according to the audit flow chart no meeting had yet taken place with the GP to agree the parameters of the initial search. The matter was not dealt with on the booking and consent form. It was also unclear why the initial search criteria were different to the nurse only audit. A nurse would then attend and complete the treatment management plan with the GP/s and finalise the Gastro Register in accordance with it. Actions would be agreed with and authorized by the GP/s. The GPSS would then attend and complete changes to the patients' medication on the computer.

The GastroCare Audit and Review detail aid (ZZOT3414) set out the reasons why an upper GI audit should be performed. These included the number of patients who could potentially benefit; GI medicines accounted for a substantial part of time and money spent on primary care; repeat prescriptions might lead to inappropriate medicines management as patients' needs changed; all primary care organisations should review the use of PPIs according to NICE guidance on the use of PPIs in the treatment of dyspepsia; and NHS performance indicators as prescribing ulcer healing drugs was one of ten indicators by which the Department of Health assessed the performance of health authorities and trusts. The detail aid explained that the audit and review would enable practices to achieve upper GI audit with minimal impact on workload; meet incentives linked to PPI prescribing; improve patient education; achieve consistency of practice prescribing and patient care; promote best practice prescribing in accordance with NICE; meet the needs of clinical governance; free up practice time; contribute to GP appraisals and provide a comprehensive review report. The detail aid stated that in the six months to September 2003 more than 300 GastroCare audits and reviews were conducted with over 8,000 patients reviewed in accordance with NICE Guidance.

The GastroCare Audit and Review booklets each left with the practice raised points similar to those in the detail aid. More emphasis was given to the NICE guidance on the use of PPIs in the treatment of dyspepsia which was described as being of particular importance. It was noted that NICE concluded that all doctors should review their use of PPIs in dyspepsia (or gastrointestinal oesophageal reflux disease (GORD)) meaning that any audit in this area would contribute to achieving national goals for prescribing. Further the availability of such guidance

made it relatively straightforward to set standards for achieving best practice.

Patients undergoing either the GPSSI or the GastroCare Audit and Review would be informed of the Wyeth GastroCare Club Patient Support Programme. This was described in the relevant practice booking and consent form as being non-promotional. The Panel did not see any of these materials.

The Panel noted that section 1 of the NICE guidance provided guidance on the use of PPIs and general dosage recommendations in specific patients groups. Section 1.7 stated that the least expensive appropriate PPI should be used. Section 5.1 stated that all doctors prescribing PPIs would need to review the indications for their use (including licensed indications and safety/side effect profile), and assess the dose used, with the aim of reducing it where appropriate. Section 8.1, Implementation, stated that primary care groups, local health groups and NHS trusts should review their current practice on the use of PPIs against section 1 of the guidance. Section 9, Clinical Audit Advice, stated that to enable clinicians to audit their own compliance with the guidance it was recommended that treatment plans be recorded for each patient with dyspepsia. This information should be incorporated into local clinical audit recording systems and consideration given to the establishment of appropriate categories in routine electronic record keeping systems.

The Panel considered this was a difficult area. It decided to consider the GPSSI service and the GastroCare Audit and Review separately. The way the services were offered ie in the context of a promotional Zoton FasTab call was not irrelevant although the Panel noted that the role of the representative was outside the scope of the complaint. The Panel noted that to benefit from the supplementary information to Clause 18.1 of the Code a service had either to enhance patient care or benefit the NHS. The Panel noted the NICE guidance.

The Panel considered that it was difficult to see how the GPSSI service would enhance patient care or benefit the NHS. The GPSSI service was offered after the GP had made the decision to switch formulation within the context of a promotional Zoton FasTab call. Whilst the medication changes were authorized by the practice it was difficult to see at what point any consideration was given to whether a change of formulation would enhance patient care or benefit the NHS. Such enhancement or benefit might, perchance, be a consequence of such a change, but the consideration of such issues did not appear to be an integral part of the service. In the Panel's view consideration of benefit to the NHS or the enhancement of patient care must be an integral and demonstrable part of the service. Whilst such factors might well be borne in mind by the prescriber such consideration did not arise as a consequence of any element of the service. This was particularly so given Wyeth's submission that the initial prescribing decision was made prior to the offer of the service. The Panel decided that the GPSSI service was not a medical and educational good or service within the meaning of the supplementary information to Clause 18.1 and thus a breach of Clause 18.1 was ruled. High standards had not been maintained; a breach of Clause 9.1 was ruled. Nonetheless the Panel did not consider that the GPSSI service reduced confidence in or brought discredit upon the pharmaceutical industry; no breach of Clause 2 was ruled.

The Panel considered that there were differences between the GastroCare Audit and Review and the GPSSI service. Consideration of some factors set out in the NICE guidance was an integral part of the GastroCare Audit and Review. The GastroCare register would continue to benefit the practice after the audit. The Panel was concerned, however, that there was no reference to prescribing the least expensive appropriate PPI. This was a significant omission given the weight attached to the NICE guidance. The Panel was also concerned that a prescribing decision had to be made prior to the offer of the service. However, the Panel considered that this was balanced by the completion of the treatment management plan. The Panel considered that, on balance, the GastroCare Audit and Review service would enhance patient care or benefit the NHS. No breach of Clause 18.1 was ruled. Consequently no breach of Clauses 9.1 and 2 was ruled.

During its consideration of this case the Panel was concerned about the explanation given for the medication change in some of the sample patient letters in the GPSSI Pack and the GastroCare Audit and Review booklets (ZZOT3415 and ZZOT3416). One letter read 'Together with the local hospital, we have carefully considered which acid-suppressing medicines are most appropriate for different conditions. As a result we have decided to prescribe X instead of Y'. Another referred to the decision resulting from discussions with local hospitals and health authority therapeutic advisors. That was not so. The Panel was also concerned that some of the materials included the statement 'Wyeth GastroCare Audit and Review is fully compliant with the ABPI Code of Practice guidelines'. This gave the misleading impression that the material had been approved by the ABPI. The Panel requested that Wyeth be made aware of its concerns.

Proceedings commenced 1 April 2005

Case completed 17 June 2005

CASE AUTH/1708/5/05

BIOGEN IDEC v SERONO

Multiple sclerosis guidelines

Biogen Idec complained about Serono's guidelines for the clinical management of multiple sclerosis (MS) patients starting Rebif (interferon beta-1a) treatment after discontinuation of Tysabri (natalizumab). Rebif was marketed by Serono and Tysabri was in clinical development with Biogen Idec and unauthorised in the UK. Serono sent the guidelines to natalizumab investigators in the UK together with a covering letter dated 15 April 2005 which stated that, due to safety concerns, the US marketing of Tysabri had been suspended as had all natalizumab clinical trials worldwide. This decision had been taken because progressive multifocal leucoencephalopathy (PML) had occurred in two patients treated with Tysabri in combination with Avonex (interferon beta-1a). The letter and the accompanying treatment guidelines recommended a way forward for treating those patients who had been enrolled in the MS Tysabri trials.

Biogen Idec submitted that all Tysabri patients in the UK were in ongoing clinical trials. The investigators had received timely and detailed information on the appropriate management of these patients; it was inappropriate for a third party to imply there was a 'recommended way forward'. These patients were still being followed up in a clinical trial and any steps taken to curtail that follow up brought discredit upon the industry and might reduce confidence in future clinical trials. Biogen Idec further alleged that as the letter encouraged the withdrawal of patients from an ongoing clinical trial, Serono had, by implication, disparaged the conduct of a Biogen Idec clinical trial. Biogen Idec also alleged that the letter was disparaging to link the uncertain aetiology of PML to the combination clinical trial of natalizumab and Avonex.

Serono's guidelines stated 'If the patient presents himself/herself with stable MS, without any clinical signs or symptoms indicative of a demyelinating event, initiation of therapy with Rebif 44mcg [sub-cutaneously, three times a week] is indicated'. Biogen Idec alleged that this statement was in breach of the Code as it was not consistent with the Rebif marketing authorization which detailed the therapeutic indications as: 'the treatment of patients with multiple sclerosis and with 2 or more relapses within the last two years'.

Biogen Idec submitted that its safety evaluation of Tysabri and any possible link to PML was ongoing. As Serono did not have access to clinical trial data it was impossible for its information to be based on an up-to-date evaluation of all the evidence and reflect that evidence clearly. Biogen Idec was not aware of any evidence to support the first point of the guidelines that 'Rebif therapy should be initiated only after at least 8 weeks off natalizumab therapy'.

Biogen Idec stated that the covering letter suggested that it was in the 'best interests of these MS patients that they continue on an effective treatment with a good safety profile…' and alleged that by implication from the next sentence in the letter this referred to Rebif. Biogen Idec noted that the Code stated that the word 'safe' must not be used without qualification, and the supplementary information clarified that the restrictions on the word 'safe' applied equally to grammatical derivatives.

Biogen Idec noted that the concluding paragraph of the guidelines mentioned 'lingering immunosuppressive effects' of natalizumab and alleged that this was unsubstantiated speculation.

Biogen Idec noted that the letter described the setting up of a registry and offered the reader the opportunity to participate. As the letter encouraged the use of Rebif, this use of a post-marketing study was clearly disguised promotion in breach of the Code.

The Panel noted that Rebif was indicated for the treatment of multiple sclerosis with 2 or more relapses within the last two years. The materials at issue only referred to MS and MS patients in general; there was no reference to relapses. Both the guidelines and the letter implied that Rebif could be used to treat all MS patients which was not so. The Panel ruled that the materials were inconsistent with the particulars listed in the Rebif SPC in breach of the Code.

The Panel considered that the content and tone of the letter implied that PML had been shown to be causally related to Tysabri therapy which was not so. The US Food and Drug Administration (FDA) had stated that the relationship between Tysabri and PML was not known but because of the rare, serious and often fatal nature of PML, use of the product had been suspended. The second paragraph of the letter at issue, which referred to the reasons for the suspension of Tysabri, did not make the whole of this position clear. The Panel considered that the letter was misleading in that regard. In the Panel's view, reference to the unknown aetiology of the observed case of PML was not sufficient to correct the misleading impression already given. A breach of the Code was ruled. The Panel further considered that to imply a proven relationship between Tysabri and PML was disparaging. A further breach of the Code was ruled. On appeal by Serono both of these rulings were upheld.

The guidelines issued by Serono stated that Rebif should be initiated only after at least eight weeks off Tysabri therapy; the document also referred to the 'lingering immunosuppressive effects from prior treatment with [Tysabri]'. The Panel noted Serono's submission that the half-life of Tysabri was 11±4 days and that it was generally accepted that it took 5 half lives before a medicine could be considered to be eliminated from the body. Given this submission the Panel did not consider that either of the above statements were unreasonable. No breach of the Code was ruled.

The Panel noted that the letter implied that Rebif had a good safety profile. Contrary to Biogen Idec's allegation, however, the Panel did not consider that the letter implied that Rebif was unequivocally safe. No breach of the Code was ruled in that regard.

The Panel did not consider that the letter or the MS treatment guidelines were disguised promotion; both were printed on Serono headed paper. Although the letter referred to the Rebif registry the Panel did not consider that the reference was such as to detract from the promotional intent of the letter. In the Panel's view recipients would not think that the materials purported to be anything other than promotional material for Rebif. No breach of the Code was ruled.

The Panel noted that the letter and treatment guidelines had been sent as a reaction to the suspension of a competitor product which was as yet unlicenced in the UK. The letter was signed by Serono's medical director for Northern Europe and as such would have a significant impact upon the recipients who would view its content as having some standing. The Panel noted, however, that it had considered the letter misleading with regard to the licenced indication of Rebif, and misleading and disparaging with regard to the safety profile of Tysabri. The Panel considered that given all the circumstances the letter brought discredit upon, and reduced the confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled which was upheld on appeal by Serono.

During its consideration of Serono's appeal, the Appeal Board expressed its extreme concern about the material at issue. This was a particularly serious matter. The Appeal Board considered that Serono should be reported to the ABPI Board of Management with the recommendation that Serono be required to publish a corrective statement.

The ABPI Board considered that this was a serious issue where it appeared aggressive marketing had been undertaken with disregard for the Code.

The ABPI Board decided that, in view of the gravity of the matter, Serono should issue a corrective statement to the doctors who had received the material at issue and be informed that any further transgression would be treated with extreme severity.

Biogen Idec complained about Serono Limited's guidelines for the clinical management of multiple sclerosis (MS) patients starting Rebif (interferon beta-1a) treatment after discontinuation of Tysabri (natalizumab). Rebif was marketed by Serono and Tysabri was in clinical development with Biogen and unauthorized in the UK. Serono sent the guidelines with a covering letter dated 15 April 2005 to natalizumab investigators in the UK. The covering letter stated that, as a result of safety concerns, the Biogen Idec Corporation had recently announced the immediate suspension in the US of the marketing of Tysabri and the suspension worldwide of dosing in all clinical trials involving natalizumab. This decision had been taken due to the occurrence of progressive multifocal leucoencephalopathy (PML) in two patients treated with Tysabri in combination with Avonex (interferon beta-1a). The letter and the accompanying treatment guidelines sought to suggest a recommended way forward for treatment of those patients who had been enrolled in the MS Tysabri trials.

Intercompany correspondence had failed to resolve the issues.

COMPLAINT

Biogen Idec submitted that all patients treated with Tysabri in the UK were participants in ongoing clinical trials. The investigators had received timely and detailed information on the appropriate management of these patients. It was inappropriate for a third party, without full access to all relevant factual information, to imply there was a 'recommended way forward'. These patients were still being followed up in a clinical trial and any steps taken to reduce the completeness of that follow up brought discredit upon the industry and might reduce the confidence in future clinical trials. Biogen Idec alleged a breach of Clause 2 of the Code.

Biogen Idec noted that Section 3 of the guidelines issued by Serono stated 'If the patient presents himself/herself with stable MS, without any clinical signs or symptoms indicative of a demyelinating event, initiation of therapy with Rebif 44mcg [sub-cutaneously, three times a week] is indicated'. Biogen Idec alleged that this was not consistent with the Rebif marketing authorization which detailed the therapeutic indications as: 'the treatment of patients with multiple sclerosis and with 2 or more relapses within the last two years'. Biogen Idec alleged a breach of Clause 3.

Biogen Idec submitted that its comprehensive safety evaluation of Tysabri and any possible link to PML was ongoing. It was reviewing clinical trial data and working with investigators to evaluate approximately 3,000 patients in multiple sclerosis, Crohn's disease, and rheumatoid arthritis trials. As Serono did not have access to these data it was impossible for its information to meet the requirements of Clause 7.2 of the Code that information claims and comparisons had to be based on an up-to-date evaluation of all the evidence and reflect that evidence clearly. The first point of the guidelines that 'Rebif therapy should be initiated only after at least 8 weeks off natalizumab therapy' was unsubstantiated; Biogen Idec was not aware of any evidence to support this assertion.

Biogen Idec stated that the covering letter suggested that it was in the 'best interests of these MS patients that they continue on an effective treatment with a good safety profile…' by implication in the next sentence in the letter referred to Rebif. Biogen Idec noted that Clause 7.9 stated that the word 'safe' must not be used without qualification, and the supplementary information clarified that the restrictions on the word 'safe' applied equally to grammatical derivatives such as 'safety'. For example, 'demonstrated safety' or 'proven safety' were prohibited under this clause.

Biogen Idec noted that the occurrence of PML in patients involved in the clinical development programme of Tysabri was the subject of an ongoing safety evaluation. The company alleged that the letter was disparaging to link the uncertain aetiology to the combination clinical trial of natalizumab and Avonex.

Biogen Idec noted that the concluding paragraph of the guidelines mentioned 'lingering immunosuppressive effects' of natalizumab. This was unsubstantiated speculation about the effects of natalizumab therapy.

Biogen Idec further alleged that as the letter actively sought to encourage the withdrawal of patients from an ongoing clinical trial, Serono had, by implication, disparaged the conduct of a Biogen Idec clinical trial.

Biogen Idec noted that the letter described the setting up of a registry and offered the 'opportunity to participate in this specific registry'. As the overall intention of the letter was to encourage the use of Rebif this use of a post-marketing study was clearly a disguised promotional activity in breach of Clause 10.2 of the Code.

RESPONSE

Serono explained that on the 28 February 2005 ongoing Tysabri trials were suspended on a worldwide basis for an indefinite period in light of the PML cases. Dosing was suspended not only in trials where Tysabri was used as part of a combination therapy with a beta-interferon, but also in those trials where it was used as monotherapy.

Following the suspension of Tysabri Serono started to receive inquiries. Doctors were legitimately considering whether, in the circumstances, there was an alternative treatment that might be provided for patients with relapsing-remitting MS who were no longer receiving any medication for their condition. It became apparent that there was concern as to whether it was appropriate to prescribe Rebif for patients who had taken Tysabri given that the patients who had suffered from PML had also taken a beta-interferon and the causal relationship, if any, between treatments and the condition was uncertain. PML was a serious and generally fatal condition and, in the light of the requests it had received for information, Serono considered it informative and responsible to develop considered guidance on switching. The guidance was drafted in collaboration with a professor of clinical neurology and an assistant professor in immunology/allergy and neurology.

There was uncertainty as to why the virus associated with PML caused active disease in some cases and the disease itself was difficult to diagnose. In the absence of any clarity as to the cause of PML and whether there was a causal contribution from the co-administration of a beta-interferon, Serono was anxious that its product Rebif (interferon beta-1a) should not become unfairly associated with any later manifestation of PML in a patient switched to Rebif. Serono therefore wished to encourage doctors to exclude the existence of PML before patients were switched (and whether those patients had been taking Tysabri alone or in combination with a beta-interferon). To do so was, in Serono's view, consistent with good practice and of benefit to patients. As a further precaution, potentially beneficial to both Serono and patients, Serono also wished to encourage very careful monitoring after treatment was initiated. The company, therefore, proposed specific pharmacovigilance activities in relation to such patients through a specific safety registry. If and when a doctor in the exercise of his professional judgment wished to prescribe Rebif to patients previously treated with Tysabri, Serono wanted to be able to point to the fact that it had given appropriate guidance on switching.

Serono stated that its letter and guidelines were sent to 20 neurologists in the UK whom it believed were likely to have a legitimate interest in the clinical management of patients who had previously received Tysabri therapy.

The objectives of the exercise were to: convey information provided by the FDA about the association (or more correctly the lack of association) based upon available evidence between PML and interferons in general; provide guidance for doctors who wished to prescribe Rebif for patients who had had their treatment stopped; emphasize the importance of taking reasonable steps to exclude PML in patients being switched and of monitoring patients whose treatment had been changed and to offer doctors the opportunity to participate in the registry set up for the purpose.

Serono stated that it took such action in order to address doctors' concerns about treatment strategy for their MS patients. It was appropriate and measured and taken following consultation with clinical experts. There was no basis for asserting that the approach taken was unethical or opportunistic. If opportunism had been the motivation Serono would have been proactive and issued a communication to doctors immediately after the suspension of dosing of Tysabri in February. Instead, the communication was reactive and issued in mid April following enquiries received from health professionals.

Serono submitted that although Biogen Idec believed that Serono was taking unfair advantage of its misfortune in relation to Tysabri, Serono believed that its actions could only be seen as reasonable. Once it was appreciated that doctors would be considering alternative therapies and Rebif would be a beta-interferon of choice for many of them, it could not be anything other than legitimate for Serono to address the issues that arose on switching in these somewhat unusual circumstances, provided the information was balanced and consistent with good clinical practice. The information provided by Serono did not run counter to good clinical practice and did not compromise patient safety. On the contrary, the guidance could only enhance patient safety. The letter expressly related the guidance to patients who had been treated with Tysabri and for whom the doctor had decided to initiate Rebif. The guidance was designed to encourage doctors to take steps to minimize the risk of PML and to detect and rule out the presence of PML before starting an alternative treatment and, thereafter, to monitor treatment closely.

Serono denied a breach of Clause 2 of the Code.

Serono noted that point 3 of its guidelines specified that 'if the patient presents himself/herself with stable MS, without any clinical signs or symptoms indicative of a demyelinating event, initiation of therapy with Rebif 44mcg sc tiw is indicated'.

PML was defined as a rare, subacute, afebrile disease characterized by areas of demyelinization surrounded by markedly altered neuroglia, including inclusion bodies in glial cells; it occurred usually in individuals with AIDS, leukaemia, lymphoma, or other debilitating diseases, or in those who had been receiving immunosuppressive treatment. It was

caused by the JC virus, a human polyoma virus. Hence, the experts that co-drafted the guidelines recommended that Rebif treatment should not be started in patients who presented with clinical signs or symptoms of a demyelinating event. That was not to say that every patient without such signs or symptoms should be prescribed Rebif. Prescription in a particular case was a matter for the doctor and the covering letter made clear that the guidance concerned cases where the doctor had decided to initiate Rebif. In so deciding the doctor would take account of the circumstances and wishes of the patient and the prescribing information.

Serono therefore did not believe that this recommendation encouraged use of Rebif other than in accordance with its marketing authorization. Each letter to doctors was accompanied by a copy of the Rebif summary of product characteristics (SPC).

Serono submitted that its communication to doctors – in so far as it referred to Tysabri – did no more than report the fact that US marketing of the product had been suspended as had clinical trial dosing worldwide. The information provided was factual and consistent with information in the public domain. Accordingly, this was not a situation where the information provided had been derived from multiple sources where evaluation of all the evidence was a relevant consideration.

Serono noted that Biogen Idec had alleged that the recommendation in the guidance that at least eight weeks should elapse before Rebif therapy was initiated in patients previously treated with Tysabri was unsubstantiated. This sensible and precautionary recommendation was made following consultation with the experts. Eight weeks was appropriate because:

a) The US Tysabri Labeling (Issue date [November/2004] I61061-1) stated that 'a mean half-life of 11 ± 4 days was observed'. The generally accepted rule in pharmacology that it took 5 times the half-life of a medicine (5 x 11 days = 55 days = 7.9 weeks) for complete elimination from the body, and so 8 weeks was an acceptable time to expect a full wash-out of Tysabri.

b) Sheremata *et al* (1999) stated that '… in those patients who received 1 and 3mg/kg Tysabri (natalizumab) in phase 1, randomized, placebo-controlled, five-level dose escalation safety, tolerability and pharmacokinetic study of a single IV dose, detectable concentrations were observed for 3 to 8 weeks'. This statement supported the application of the five half-lives rule, and therefore, the advice to wait at least 8 weeks after discontinuation of Tysabri before starting another MS therapy.

Serono noted Biogen Idec's suggestion that Clause 7.9 prohibited use of the phrase 'good safety profile'. Clause 7.9 required the word 'safe' or derivatives thereof to be qualified. This meant that one could not state a product was safe or make claims which were tantamount to claiming a product was safe eg 'demonstrated safety' or 'proven safety'. Clause 7.9 did not prevent a product's safety profile being described as good or the like provided such a claim could be substantiated. Stating that a product had a good safety profile was not the same as stating that it was completely safe, which was what Clause 7.9 of the Code was designed to prevent.

Serono acknowledged that PML occurred in the combination trial of Tysabri and Avonex. Biogen Idec's letter merely reported that the aetiology of the PML events in the combination trial was uncertain. This was factually accurate. The statement reflected comment from the FDA, for example, that 'the relationship between Tysabri and PML is not known at this time' and 'the relationship between use of Tysabri and PML is not clear'. Moreover, it was entirely consistent with the Biogen Idec/Dear Doctor letter which stated that 'the factors leading to activation of the latent infection are not fully understood'.

Serono did not consider that Clause 8.1 of the Code prohibited comment which was accurate. Disparaging comments aimed to bring discredit upon the object of them. Nothing stated by Serono disparaged Biogen Idec or its products. The events referred to were facts, accurately and neutrally described. Serono did not suggest that the manifestation of possible PML was anyone's fault.

The concluding paragraph of Serono's guidelines did not state that there were, or would be, lingering immunosuppressive effects from Tysabri therapy. Natalizumab was a selective immunosuppressive agent and the guidance advised doctors that conducting a full blood count would enable determination of whether a patient was still immunosuppressed. This was relevant because a suppressed immune function might be one reason why PML developed. Furthermore, it had been demonstrated that, lymphocyte, monocyte and eosinophil counts increased in patients taking Tysabri therapy suggesting an effect on the immune system. The uncertain aetiology of the association of Tysabri in combination with interferons could not be excluded.

Serono therefore considered that the statement in its guidance was fair and balanced on the evidence available and it was reasonable to include some background in order to put the sensible precautions set out in the guidance in their proper context.

Serono was not seeking the withdrawal of patients from an ongoing clinical trial. As referred to above, ongoing trials had been suspended for an indefinite period and physicians were obliged to and were legitimately considering whether, in the circumstances, there was an alternative treatment that might be provided for patients who were currently not receiving any medicine for their condition. The guidelines were expressly related to cases where the doctor had already decided to switch a patient to Rebif and Serono had a legitimate interest in advising on issues that should reasonably be considered. Serono presumed that Biogen Idec was not suggesting that it was inappropriate for doctors to decide that it was in the interests of patients to initiate an alternative approved product when the choice was to leave a patient without any treatment. Contrary to a suggestion made by Biogen Idec that Serono was advised prior to sending out its letter to neurologists

that the issue of switching and appropriate guidance was in hand, Serono submitted that it was never advised before its letter was sent of Biogen Idec's intentions. Indeed, even after Biogen Idec had complained to Serono about its letter, it refused to provide Serono with any information about guidelines that it had or might issue itself.

Serono stated that since PML was a serious and generally fatal condition its view, as a responsible company, was that it was essential that patients taking Rebif who had been previously treated with Tysabri were very carefully monitored.

Serono acknowledged that its letter fell within the scope of the Code but did not accept that the registry was a promotional activity. Patient registries were legitimate pharmacovigilance tools which companies were increasingly encouraged to use by regulatory authorities because they enabled early detection of safety signals in normal practice. In this case, the registry was initiated as a result of the potential public health risk identified in the combination trial of Tysabri and Avonex and subsequently in a trial where Tysabri was used as monotherapy. The registry was designed to contribute to the knowledge base relating to PML and interferon use. To date, there was no evidence that PML was linked to Rebif, but from a risk-management perspective, Serono considered it sensible to seek to capture outcome data from patients that switched to Rebif following use of Tysabri. The registry was non-promotional. Participation was voluntary and there was no incentive associated with participation.

Serono noted that Biogen Idec had stated that Serono's actions might undermine the conduct of ongoing trials and interfere with the collection of information required by regulatory authorities. It was not clear to Serono how its activities would undermine the conduct of the Tysabri trials or interfere with collection of information; Biogen Idec had not sought to explain why it believed this to be the case. The ICH good clinical practice guidelines provided that if a trial was suspended for any reason, the investigator/institution should promptly inform the trial subjects and should assure appropriate therapy and follow-up for the patients. Serono stated that its approach was consistent with good clinical practice. Whether neurologists were inclined to agree with the guidelines or disagreed and followed their own judgment or any guidelines that might be suggested by Biogen Idec, the fact that Serono issued its guidance to neurologists did not, of itself, undermine the conduct of the trial or render its guidelines inconsistent with good clinical practice.

PANEL RULING

The Panel noted from intercompany correspondence written by Biogen Idec that Tysabri was approved in the US but not in Europe and that in the UK there was one patient in the combination trial for whom Tysabri dosing had been suspended.

Serono had written the material at issue, MS guidelines and a covering letter, as a result of receiving enquiries subsequent to Biogen Idec's suspension of Tysabri trials in the UK. The letters, however, were not replies in response to individual enquiries and so could not claim the exemption to promotion for such activity as detailed in Clause 1.2 of the Code. The guidelines and the letter were thus promotional materials for Rebif and needed to comply with all of the relevant requirements of the Code.

The Panel noted that the Rebif SPC (ref emc.medicines.org.uk) stated that the product was indicated for the treatment of multiple sclerosis with 2 or more relapses within the last two years. The materials at issue only referred to MS and MS patients in general; there was no reference to relapses. Both the guidelines and the letter implied that Rebif could be used to treat all MS patients which was not so. The Panel considered that the materials were thus inconsistent with the particulars listed in the Rebif SPC. A breach of Clause 3.2 was ruled. This was accepted by Serono.

The Panel considered that whether it had access to Tysabri clinical trial data or not, whatever Serono stated in its letter must comply with the Code. The content and tone of the letter implied that PML had been shown to be causally related to Tysabri therapy which was not so. A statement issued by the FDA noted that the relationship between Tysabri and PML was not known but because of the rare, serious and often fatal nature of PML, use of the product had been suspended. The second paragraph of the letter at issue, which referred to the reasons for the suspension of Tysabri, did not, however, make the whole of this position clear. There was no information to allow the reader to judge the clinical significance of the situation. The Panel considered that the letter was misleading in that regard. In the Panel's view, reference in the fourth paragraph of the letter to the unknown aetiology of the observed case of PML was not sufficient to correct the misleading impression already given. A breach of Clause 7.2 was ruled. The Panel further considered that to imply a proven relationship between Tysabri and PML was disparaging. A breach of Clause 8.1 was ruled. These rulings were appealed.

The guidelines issued by Serono stated that Rebif should be initiated only after at least eight weeks off Tysabri therapy; the document also referred to the 'lingering immunosuppressive effects from prior treatment with [Tysabri]'. The Panel noted Serono's submission that the half-life of Tysabri was 11±4 days and that it was generally accepted that it took 5 half lives before a medicine could be considered to be eliminated from the body. Given this submission the Panel did not consider that either of the above statements were unreasonable. No breach of Clause 7.2 of the Code was ruled.

The Panel noted that the letter implied that Rebif had a good safety profile. Contrary to Biogen Idec's allegation, however, the Panel did not consider that the letter implied that Rebif was unequivocally safe. No breach of Clause 7.9 was ruled in that regard.

The Panel did not consider that the letter or the MS treatment guidelines were disguised promotion; both were printed on Serono headed paper. Although the letter referred to the Rebif registry the Panel did not consider that the reference was such as to detract from

the promotional intent of the letter. In the Panel's view recipients would not think that the materials purported to be anything other than promotional material for Rebif. No breach of Clause 10.2 was ruled.

The Panel noted that the letter and treatment guidelines had been sent as a reaction to the suspension of a competitor product which was as yet unlicensed in the UK. The letter was signed by Serono's medical director for Northern Europe and as such would have a significant impact upon the recipients who would view its content as having some standing. The Panel noted, however, that it had considered the letter misleading with regard to the licenced indication of Rebif, and misleading and disparaging with regard to the safety profile of Tysabri. The Panel considered that given all the circumstances the letter brought discredit upon, and reduced the confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled. This ruling was appealed.

During its consideration of this case the Panel noted that neither the guidelines nor the accompanying letter included the Rebif prescribing information. Although the items had been sent with a Rebif SPC this was not sufficient to satisfy the requirements of Clause 4.1 of the Code. The Panel asked that Serono be advised of its concerns in this regard.

APPEAL BY SERONO

Serono did not accept that the content of the letter was misleading as alleged. The letter made a factual statement that dosing in the trials was suspended because of the occurrence of PML in three patients. It was not stated that a causal relationship had been proven between Tysabri and PML, and any inference as to the level of suspicion that such a relationship existed went no further than statements by the FDA, which it was not suggested were unfair or unbalanced. Serono submitted that in fact, it was axiomatic that if, in a clinical trial population where a new therapy was being tested, there had been three serious adverse events of the same nature and the adverse event was highly unusual, the temporal relationship supported a possible causal relationship between the medicine and the event. A temporal relationship in such a case was the most important factor to consider in assessing causality. This was why the regulators and Biogen Idec was of the view that dosing should be suspended. The letter did not go beyond reporting that temporal relationship and did not suggest that the pathophysiological mechanism by which Tysabri might lead to PML had been established. On the contrary, the letter faithfully reported the FDA's Public Health Advisory by stating that the aetiology of PML was uncertain. The fact that other medical commentators had said that the available data pointed rather strongly to the existence of a causal relationship between treatment with natalizumab and the occurrence of PML, reinforced the conclusion that it was not unreasonable of Serono merely to report the FDA's position. In his editorial entitled 'Patients at Risk' published on the website of the New England Journal of Medicine of 9 June 2005, Dr J M Drazen reviewed the situation and wrote that 'Given these data, the association between treatment with natalizumab and PML seems clear'. Similarly, the summary of Case Report by Dr G Van Assche *et al* (2005) also published on the website of the New England Journal of Medicine on 9 June 2005 concluded: 'This case report, along with two others, suggests that anti-alpha4-integrin therapy can result in JC-virus-induced PML'.

Serono noted that the Panel had noted the FDA statement that PML was a rare, serious and often fatal condition and, therefore, that the trials had been suspended, although the relationship between Tysabri and PML was not known. The Panel's ruling appeared to suggest that Serono's letter was misleading because it did not emphasise the lack of certainty as to the precise relationship, and, as a consequence, the reader did not have sufficient information to enable him to judge the clinical significance of the situation. Serono respectfully considered that this criticism was unjustified. First, the immediate clinical significance of the situation was not in doubt. The evidence of a link was sufficient for the supply of a product, including for on-going trials, to be suspended. In considering whether a statement was misleading all the circumstances must be taken into account. The communication was sent to an expert audience, already apprised of the suspension of the trial. The recipients of the letter would have been well aware that PML was a serious, often fatal, condition and the letter made clear that the cases giving rise to the suspension of the trial were fatal. The level of suspicion that the association was causal was high enough to justify the voluntary and wholly responsible suspension by Biogen Idec.

Serono submitted that accordingly, given the context in which the guidelines were provided, the clinical significance of the situation would have been obvious and it was at a loss to see why it was necessary, for it, to say more than was stated by the FDA. The mechanism might be unclear and any pre-disposing factors might be unclear, but the clinical implications were clear enough without requiring Serono to elaborate on what the FDA had said. This was otherwise not a case where the science or issues were complicated or obscure. Patients being treated with a combination of a new monoclonal antibody for multiple sclerosis and an established beta-interferon were diagnosed with PML. One patient receiving the monoclonal antibody as monotherapy was also diagnosed with PML. Clearly, in such circumstances, the concern was that the likelihood of a causal relationship between the trial medication and the condition was sufficient to dictate the course Biogen adopted.

For the reasons stated above, Serono did not accept that it had implied a proven relationship between Tysabri and PML. Serono's letter was factual and accurate and there was no statement made in the letter which criticised or denigrated either Biogen Idec or its product, Tysabri. It could not be denigrating of Biogen Idec or its product to report the fact of what had happened in relation to a trial and the statements made by the FDA. Merely setting out the facts, even if those facts did suggest the existence of a probable

(but not certain) association between the product and the event, did not amount to disparaging the product. If this were the case, much of the comparative advertising that was engaged in by the industry would be in danger of being found in breach of Clause 8.1, even if it presented facts accurately.

In its ruling the Panel accepted that Serono had written to doctors to provide guidelines for the clinical management of those MS patients whom doctors were minded to switch to Rebif treatment after discontinuation of Tysabri, following enquiries the company had about whether it was appropriate to switch patients in this way. In two of the three cases of PML Tysabri had been co-administered with a beta-interferon and it was therefore not surprising for questions to be raised about whether there could be any causal contribution from the beta-interferon element of the treatment. The possibility of product liability claims (however unmeritorious) was of increasing concern to all companies today. Serono was concerned that its product, Rebif (also a beta-interferon), should not end up after such a switch, being associated with PML by chance alone.

Serono submitted that following expert advice the best way to ensure this did not happen was to encourage doctors who had decided to initiate treatment with Rebif to undertake diagnostic tests to exclude the existence of PML prior to starting treatment and to allow an appropriate wash-out period after cessation of Tysabri and before initiation of Rebif. The Panel seemed to attach importance to the fact that the letter sent by Serono was signed by a medical director and as such would have been treated as important by recipients. But the issue of ensuring that any switch to Rebif was undertaken in accordance with the above safeguards was a medical matter. It was important to Serono and had been discussed at length by Serono's medical department. In Serono's eyes it was entirely appropriate to send the letter enclosing the clinical management guidelines from the medical director.

With regard to the Panel's statement that in the UK there was one patient in the combination trial for whom Tysabri dosing had been suspended, Serono submitted that the Panel might have gained a false impression of the UK element of the study. Several tens of patients participated in Tysabri trials in the UK and dosing was not only suspended in the combination trial, but also in all monotherapy trials.

Serono submitted that it had not intended to suggest that Rebif should be used otherwise than in accordance with its licensed indication and, as noted in its response to the complaint, the SPC was sent to doctors with the letter and the guidelines. Moreover, paragraph 3 of the guidelines which was the subject of the complaint had in fact been amended by Serono prior to the complaint (but after the UK mailing took place) to make it clear that initiation of therapy with Rebif should be in accordance with the SPC. A copy of the amended guidelines was provided. Serono had not appealed the finding of a breach in this regard because it recognised that it had failed to spot the issue. But it did not consider that this failure was at the very serious end of the spectrum of possible breaches of Clause 3.2. There was no evidence that any of the relatively few physicians who received the letter were misled and indeed this was most unlikely given the highly expert nature of the investigator group to whom the guidelines were addressed.

Serono noted that as regards the allegation concerning failure to put the reports of PML in adequate clinical context and the allegation of disparagement of Tysabri's safety profile, it had explained its position above. On this occasion the Panel's assessment was in error. However, whether or not, on reflection, the Appeal Board considered the Panel's ruling on these points to be correct, these could not fairly be viewed as plain, serious and irresponsible breaches of the Code.

Serono noted that a ruling of a breach of Clause 2 was a sign of particular censure and was reserved for exceptional circumstances. Accordingly, Serono submitted that it was extremely surprised that the Panel had determined that the breaches at issue equated to a breach of Clause 2. In previous cases, a breach of Clause 2 had only been found where a company's conduct was very obviously conduct that discredited the industry or brought it into disrepute. Examples were where the conduct compromised patient safety, where a company continued to engage in activity which had previously been ruled to be in breach of the Code, or where the activity engaged in by the company would not pass the so-called 'red face' test, such as those cases where meetings were held in order to create an opportunity to provide participants with lavish hospitality, or the arrangements put in place by a company fettered a doctor's freedom to prescribe. Serono also accepted that where the Panel had found that a company had breached a significant number of clauses of the Code and those breaches were serious, the cumulative effect might amount to the breach of Clause 2. However, this was not such a case. The arrangements initiated by Serono were designed firstly to ensure that if a doctor decided to switch patients to Rebif precautions were taken to confirm such patients did not have PML and secondly in view of the seriousness of the issue, to enhance Serono's pharmacovigilance activities with regard to its beta-interferon. There was no evidence that the arrangements either interfered with, or compromised, any follow-up conducted by Biogen. If the Panel ruled breaches of Clause 2 in situations which, on an objective view, did not require particular censure, the value of retaining Clause 2 as an indication of particular censure was diminished.

COMMENTS FROM BIOGEN IDEC

Biogen Idec noted that Serono had maintained that its letter was not misleading as to the implication of a causal relationship between Tysabri and PML. The appeal had stated that Serono 'faithfully reported the FDA's Advisory'. However Biogen Idec alleged that a review of the statements posted on the FDA website showed that Serono had failed to accurately represent the FDA statements.

Biogen Idec noted that the FDA Alert stated 'the two confirmed cases of PML do not necessarily represent a causal association between the use of this agent and PML' and it continued, 'additional information needs

to be obtained to fully understand the connection'. Serono's original letter included an un-referenced statement 'given the uncertain etiology of these serious and life threatening events in the combination clinical trial of natalizumab with Avonex …'. This un-referenced statement could not be considered to be an accurate and faithful reproduction of the FDA's statement.

Biogen Idec noted that Serono had also noted that its 'letter makes clear that the cases giving rise to the suspension of the trial were fatal'. This was inaccurate. One of the two patients treated with natalizumab in combination was still alive. This was clearly stated in the FDA Alert. The third case of PML was described by Serono as 'another lethal case'. Biogen Idec alleged that Serono's factually inaccurate and selective presentation of material from the FDA did not provide the reader with sufficient information to judge the clinical significance of the situation and sought to deliberately mislead with the overt or covert objective of trying to secure commercial gain for Rebif.

Biogen Idec noted that Serono's appeal sought to introduce editorials and articles published in the New England Journal of Medicine in order to try and justify its position retrospectively. Biogen Idec noted that these materials were not published until 9 June 2005, eight weeks after the breach had occurred. In line with previous Appeal Board decisions (eg Case AUTH/1574/4/04) Biogen Idec trusted that the Appeal Board would not take these documents into account during its deliberations.

Biogen Idec noted that Serono maintained that its letter was sent to an 'expert audience'. However, Biogen Idec alleged that the selection process for recipients of this letter was not clear. In the UK there were 13 investigators involved in the clinical trials with natalizumab; furthermore, only one site had enrolled a patient in the combination study. In Serono's response to the complaint it had confirmed that it had sent its letter to 20 neurologists in the UK, clearly a wider distribution than the study investigators.

Biogen Idec alleged that the final two paragraphs of the appeal continued to adopt a position that did not reflect accurately the prevailing situation on 15 April 2005. Serono had stated that, 'the immediate clinical significance of the situation was not in doubt', that there was 'evidence of a link' and the 'clinical significance of the situation will have been obvious'. The reality of the situation was that serious adverse events had been reported in the context of clinical trials with natalizumab. A causal relationship had not been established. Consequently, a comprehensive safety evaluation had begun in order to fully investigate it. All investigators had received comprehensive information from Biogen Idec in a memorandum sent with supporting information on 23 March 2005.

Biogen Idec noted that Serono was made aware of this situation during an exchange of telephone calls.

Biogen Idec noted that Serono had claimed that it was not disparaging and it did not accept that it had implied a proven relationship between natalizumab and PML. As previously stated above, Biogen Idec disagreed that Serono's letter 'faithfully reported the FDA's Advisory'. Biogen Idec agreed with the Panel's finding of a breach of Clause 7.2 and found nothing in Serono's appeal that would suggest a re-evaluation of that finding. On the contrary, Biogen Idec found it perplexing that Serono found its disparaging inferences consistent with standards of comparative advertising in the pharmaceutical industry.

Biogen Idec noted that Serono had admitted to having breached Clause 3.2. Whilst Serono acknowledged that if had they altered paragraph 3 of the guidelines after the UK mailing took place, Biogen Idec was not aware that Serono had taken any steps to correct this error with the recipients of its original correspondence. This suggested both a deficiency in internal certification processes and a lack of true commitment to adhere to both the spirit and the letter of the Code. Biogen Idec stated that it was not appropriate for Serono to determine the seriousness of any breach but to respect the Panel's assessment in this regard.

Biogen Idec noted that Serono's response to the complaint had also implied that it had acted 'reactively' under Clause 1.2. This was clearly not the case, as this correspondence was not sent in response to individual enquiries but to those neurologists who Serono deemed to have a legitimate interest in the clinical management of patients who had previously received natalizumab. The Panel had ruled already that Serono could not claim exemption to promotion under Clause 1.2 of the Code and that its letter and guidelines were promotional.

Biogen Idec noted that Serono, had sought to classify the recipients of the letter as a relatively few members of an investigator group. As the rationale behind the process for recipients of the letter was not made clear, Biogen Idec alleged that, it was totally inappropriate for Serono to seek to downplay the potential impact of its targeted communication.

The letter and accompanying treatment guidelines had been sent clearly as a direct reaction to the suspension of natalizumab. The letter was signed by Serono's medical director of Northern Europe and thus the recipients would review its content as having some considerable standing. Serono, by omission of prescribing information and by using a medical signatory, appeared to have been trying to disguise this opportunistic promotional activity as the dissemination of independently endorsed treatment recommendations.

In summary, Biogen Idec agreed with the Panel's assessment that Serono's letter was misleading, disparaging and brought discredit upon and reduced confidence in the pharmaceutical industry, there was no material in the appeal that justified the reversal of this judgement.

APPEAL BOARD RULING

The Appeal Board's decision about the material at issue would be based on the information available at the time the letter was sent (15 April 2005). It thus disregarded the material published in the NEJM in June 2005.

The Appeal Board noted the submission of Biogen Idec's representatives that, further to its voluntary suspension of Tysabri trials in the UK, there had been an emergency amendment to the study protocol to enable patients to receive another MS medicine. The company had not issued any specific recommendations about future treatment options or advice about the washout period. The company representatives submitted that Biogen Idec was unable to do so until the ongoing safety evaluation was complete. The Appeal Board considered that the absence of such advice would have left clinicians in a very difficult situation with little information as to how to treat their patients. Serono had written the material at issue, MS guidelines and a covering letter, as a result of receiving enquiries subsequent to Biogen Idec's suspension of Tysabri trials in the UK. The Appeal Board noted from the Serono representatives that the centres to which the guidelines had been sent had been based upon advice sought from its sales representatives that they were the Tysabri trial centres. The Appeal Board noted that the letters were unsolicited; they were not replies in response to individual enquiries and so could not claim the benefit of the exemption to promotion for such activity set out in Clause 1.2 of the Code. The guidelines and the letter were thus promotional materials for Rebif and needed to comply with all of the relevant requirements of the Code.

The Appeal Board noted the statement issued by the FDA that the relationship between Tysabri and PML was not known, but because of the rare, serious and often fatal nature of PML, use of the product had been suspended. The second paragraph of Serono's letter, which referred to the reasons for the suspension of Tysabri, was not a fair reflection of the position. The content and tone of the letter implied that PML had been shown to be causally related to Tysabri therapy which was not so. There was no information to allow the reader to judge the clinical significance of the situation. The Appeal Board considered that the letter was misleading in that regard. In the Appeal Board's view, reference in the fourth paragraph of the letter to the unknown aetiology of the observed case of PML was insufficient to negate the misleading impression already given. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful. The Appeal Board further considered that to imply a proven relationship between Tysabri and PML was disparaging as alleged and upheld the Panel's ruling of a breach of Clause 8.1. The appeal on this point was unsuccessful.

The Appeal Board noted that the letter and treatment guidelines had been sent as a reaction to the suspension of a competitor product which was as yet unlicensed in the UK. The letter was signed by Serono's medical director for Northern Europe and as such would have a significant impact upon the recipients who would view its content as having some standing. The Appeal Board noted, however, that the Panel had ruled the letter misleading with regard to the licensed indication of Rebif. This ruling had been accepted by Serono. The Appeal Board had upheld the Panel's rulings that the letter was misleading and disparaging with regard to the safety profile of Tysabri. The Appeal Board considered that given all the circumstances the letter brought discredit upon, and reduced the confidence in, the pharmaceutical industry and upheld the Panel's ruling of a breach of Clause 2. The appeal on this point was unsuccessful.

The Appeal Board was extremely concerned about the material. This was a particularly serious matter. The Appeal Board considered that Serono should be reported to the ABPI Board of Management in accordance with Paragraph 12.2 of the Constitution and Procedure with the recommendation that Serono be required to publish a corrective statement.

REPORT FROM THE APPEAL BOARD TO THE ABPI BOARD

The ABPI Board considered that this was a serious issue where it appeared aggressive marketing had been undertaken with disregard for the Code.

The ABPI Board considered that in view of the gravity of the matter the appropriate sanction would be to require Serono to issue a corrective statement. The corrective statement should be sent directly to the doctors who had received the material at issue or as part of a publication distributed mainly to those doctors. The ABPI Board decided that Serono should be informed that any further transgression would be treated with extreme severity.

Complaint received	**11 May 2005**
PMCPA proceedings completed	**5 October 2005**
ABPI Board proceedings completed	**5 December 2005**

CASE AUTH/1717/6/05

PFIZER v YAMANOUCHI PHARMA

Vesicare leavepiece

Pfizer complained about superiority claims made in a Vesicare (solifenacin) leavepiece issued by Yamanouchi Pharma (now Astellas Pharma) which discussed the results of the STAR study wherein Vesicare was compared with tolterodine extended release (Pfizer's product, Detrusitol XL) in patients with overactive bladder syndrome (OAB). The results of the STAR study did not demonstrate superiority. From the primary endpoint, it was clear that Vesicare was non-inferior to tolterodine XL. Pfizer alleged that it was not statistically accurate to make superiority claims from the secondary endpoints; such claims were misleading and incapable of substantiation.

The Panel noted that the front cover of the leavepiece read 'New in overactive bladder New in flow control'. Text within a pink star read 'New data: superiority vs tolterodine XL'. The strapline beneath the product logo read 'Early results, continuing success'. 'Star – A landmark Vesicare study' in emboldened type headed page two which set out the study objective and design. The study objective read 'To assess the efficacy of a flexible dose regimen of once daily Vesicare 5mg or 10mg compared to once daily tolterodine XL 4mg in patients with Overactive Bladder symptoms'. Page three was headed 'Vesicare – superior efficacy in …' beneath which comparative data for urgency episodes/24 hrs and incontinence episodes/24hrs were presented in two bar charts. Bullet points then noted that statistically significantly more incontinent patients became dry on Vesicare and pad usage per 24 hours was reduced in the Vesicare group compared with those on tolterodine XL; withdrawal rates due to adverse effects was comparable in the two groups.

The Panel considered that the leavepiece was not a fair reflection of the STAR study. There was no mention of the primary finding of non-inferiority with regard to frequency of micturition. The overall impression was that Vesicare was unequivocally superior to tolterodine XL on all parameters and that was not so. The leavepiece was misleading in this regard and breaches of the Code were ruled.

Pfizer stated that to achieve the double-dummy design in the STAR study, Pfizer's tolterodine XL capsules were over-encapsulated into a 'blank'. The leavepiece featured the claim that 'Vesicare was superior (p=0.0059) to tolterodine XL in reducing incontinence episodes'. Pfizer noted that a bioequivalence study was not undertaken. It was concerned that the over-encapsulation might have compromised the clinical profile of tolterodine XL. Pfizer noted that results from other studies appeared to demonstrate better results than that demonstrated in the STAR study.

With reference to the regulatory guidance for modified release capsules, Pfizer understood that bioequivalence data was required as tolterodine XL had been over-encapsulated and co-administered with two placebo tablets. Pfizer alleged that as bioequivalence had not been confirmed, it was not possible to claim that Vesicare was more effective than tolterodine XL as the comparison was clearly invalid. Any such claims were therefore invalidated by the inadequacy of the clinical trial.

The Panel noted Astellas' submission that the *in vitro* dissolution data met the recommended conditions in three sets of regulatory guidance. The Panel also noted that some of the studies referred to by Pfizer had variously used reported median reductions in daily or weekly events as opposed to the mean reduction in daily events reported in the STAR study. Although one study had reported mean reduction in daily events, the study was open-label as opposed to the double-blind, double-dummy design of the STAR study. The Panel did not consider, on the basis of the evidence before it, that the encapsulation of the tolterodine XL had resulted in a decrease in its efficacy. On this basis the Panel ruled no breaches of the Code. The Appeal Board upheld these rulings on appeal by Pfizer.

Pfizer stated that Vesicare was available in two doses (5mg and 10mg). The results presented in the STAR study represented the pooled results ie at the end of this study there was a treatment arm of patients who completed on solifenacin 5mg and a treatment arm that started on 5mg and titrated to 10mg. It was thus difficult to determine what the actual profile was of either dosage. It was conceivable that 5mg solifenacin would cause fewer adverse events. Hence, the pooling of the results would present a more favourable tolerability profile. Pfizer considered that the results of both the 5mg and the dose titration to 10mg should be presented separately in a way in which health professionals could reliably understand the results. Pfizer therefore alleged that this omission in the presentation of the data and the pooling of results was selective and the basis for misleading superiority claims.

The Panel noted that the primary objective of the STAR study was to assess the efficacy of a flexible dose regimen of Vesicare 5mg or 10mg once daily compared to tolterodine XL 4mg once daily in patients with OAB. Patients could request a dose increase after four weeks of active treatment, the decision on whether to increase a patient's dose was made jointly by the investigator and patient. Page two of the leavepiece headed 'STAR – A landmark Vesicare study' explained the study objective and referred to the flexible dose regimen. A graphical representation of the study design clearly set out the dosing regimen of each study arm over the 12 week study period. Two bar charts on the facing page made it sufficiently clear that the Vesicare data related to the 5/10mg od dosing regimen. Similarly, the final bullet point on that page which discussed comparable withdrawal rates for adverse events stated that the Vesicare data was for the 5mg/10mg groups combined.

The Panel noted that the Vesicare data was not pooled as alleged by Pfizer. The flexible 5mg/10mg

dosing arm was one treatment arm of a two arm study. The flexible dosing arm was not a dose titration posology. According to its summary of product characteristics (SPC) the recommended dose of Vesicare was 5mg once daily. If needed the dose might be increased to 10mg once daily. The Panel considered that it was sufficiently clear that the data presented in the leavepiece related to the 5mg/10mg flexible dosing arm of the study and did not consider it misleading or incapable of substantiation on this point as alleged. No breach of the Code was ruled.

Pfizer alleged that tolterodine XL was disparaged in the presentation of the STAR results. The Panel did not consider that the leavepiece disparaged tolterodine XL and no breach of the Code was ruled in that regard.

Pfizer Limited complained about a leavepiece (ref YAM67288) issued by Yamanouchi Pharma Ltd (now known as Astellas Pharma Ltd) in relation to Vesicare (solifenacin). The leavepiece presented data from the STAR study wherein Vesicare was compared to tolterodine extended release (Pfizer's product, Detrusitol XL) in patients with overactive bladder syndrome (OAB).

General comments by Pfizer

Pfizer explained that the STAR study was a 12 week, double-blind, double-dummy, randomised, head-to-head study comparing 5mg and 10mg Vesicare with tolterodine 4mg XL.

The primary endpoint in this study was micturition frequency; Vesicare (5mg/10mg) was shown to be non-inferior to tolterodine 4mg XL. There were various secondary endpoints in this study in which Vesicare was statistically significantly different compared with tolterodine 4mg XL. Analysis of the adverse events in this study showed that dry mouth and constipation were more common with Vesicare compared with tolterodine 4mg XL (30% vs 24.1% and 6.4% vs 2.1% respectively).

General comments by Astellas

Astellas explained that OAB was a common, chronic, distressing, debilitating, undignified condition. It was estimated that between 50 and 100 million people suffered from it worldwide. It was more common in women than in men and the incidence increased with age. A survey of more than 16,000 people aged ≥ 40 years, conducted in 6 European countries, showed that OAB affected nearly 17%, predominantly women.

The International Continence Society (ICS) describe the OAB as *'urgency, with or without urge incontinence, usually with frequency and nocturia'* (Abrams *et al* 2003 and Chapple *et al* 2005).

Although frequency was not defined as the leading symptom, it was often used in regulatory studies as the primary endpoint because of its relative objectivity for measuring efficacy. However urgency often led to the other symptoms of OAB.

Astellas stated that Vesicare was licensed for 'symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder syndrome'. 'The recommended dose is 5mg solifenacin once daily. If needed, the dose may be increased to 10mg solifenacin once daily'.

The primary objective of the STAR study was to assess the efficacy of a flexible dose regimen of Vesicare 5mg or 10mg (2 x 5mg) once daily compared to tolterodine XL 4mg once daily in patients with OAB. Secondary objectives were to assess and compare the safety and tolerability of the two treatments and to determine the percentage of patients who required a dose higher than 5mg Vesicare or 4mg tolterodine XL.

Patients (male and female 18 years and over) who had a ≥ 3 month history of OAB symptoms including urinary frequency, urgency or urge incontinence, entered a two-week, placebo run-in phase. Those experiencing a micturition frequency on average of ≥ 8 per 24 hours, and at least 3 episodes of urgency or urinary incontinence, during the 3 day diary period, were randomised to receive either Vesicare 5mg (group 1) or tolterodine XL 4mg once daily (group 2). As the study was double-blind and double-dummy patients took three pills once daily from the outset. After randomisation, group 1 took 1 placebo capsule, 1 placebo tablet and 1 active tablet (Vesicare 5mg) and group 2 took 1 active capsule (tolterodine XL 4mg) and 2 placebo tablets.

Patients could request a dose increase after four weeks of active treatment; the decision on whether to increase a patient's dose was made jointly by the investigator and patient. Those in group 1 who increased dose were then given 2 active tablets (2 x 5mg Vesicare tablets) plus 1 placebo capsule (group 1A) and those who continued on Vesicare 5mg were called group 1B. Patients in group 2 were already receiving tolterodine XL at the only UK licensed dose (4mg), and so if they requested a dose increase they had a pseudo-increase (group 2A) and did not receive an increase in active medication. Therefore patients in group 2A and those who did not request an increase in dose (group 2B) continued on the same dose as previously; 1 active capsule (4mg tolterodine XL) and 2 placebo tablets. Therefore, when patients had a dose increase (or pseudo-increase) no extra 'pills' were taken.

Treatment was continued at the original or increased dose for a further eight weeks.

As specified in the protocol, the primary efficacy analysis was to test for non-inferiority in the change in mean number of micturitions from baseline per 24 hours based on the per protocol set. This was tested using an ANCOVA model.

The secondary efficacy analyses were to test for superiority in terms of improvement from baseline per 24 hours in mean number of urgency episodes, urge incontinence episodes, volume voided, incontinence episodes, nocturia episodes, micturition frequency, pad use, 50% incontinence reduction, and percentage of patients dry in a three day diary period. Patient reported outcomes were assessed by patient perception of bladder condition and patient assessment of treatment benefit. Physician assessment

of treatment benefit was also measured. As specified in the protocol, secondary efficacy analyses were undertaken on the full analysis set (FAS) using a two-sided ANCOVA model. The FAS was a modified Intention to treat (ITT) population that excluded patients with no baseline data.

One hundred and seventeen sites in 17 European countries randomised 1200 patients to either Vesicare (n=593) or tolterodine XL (n=607). The FAS comprised 1177 patients (Vesicare (n=578) or tolterodine XL (n=599)). The per protocol set comprised 1049 patients (Vesicare (n=525) or tolterodine XL (n=524)).

The primary efficacy analysis (micturition frequency) demonstrated that Vesicare was not inferior to tolterodine XL 4mg (p=0.0041).

It was pre-defined that Vesicare, with a flexible dosing regime, would be tested for superiority in ten parameters. It was found to be superior (improvement in OAB symptom indicated by statistical significance) to tolterodine XL in the following parameters:

- urgency episodes (p=0.0353)
- urge incontinence episodes (p=0.001)
- incontinence episodes (p=0.0059)
- volume voided (p=0.0103)
- pad usage (p=0.0023)
- percentage of dry patients (p=0.0059)
- percentage of patients showing 50% reduction in incontinence episodes (p=0.0212)
- patient perception of bladder condition (p=0.0061).

Superiority was not shown for the parameters of micturition frequency and nocturia episodes in the defined model. When given the opportunity at week four, 48% of patients on Vesicare 5mg requested an increase in dose compared with 51% of patients on tolterodine XL 4mg.

In response to a request for further information Astellas explained that the company study report had just been finalised and the STAR study had become available online in European Urology as an article in press. However, these documents were not available at the time of approval of the leavepiece. Copies of the relevant materials available at that time were provided.

The statistical tables provided were the raw output from the statistical analysis programme (SAS). The descriptor 'pooled' had been used in this programme to indicate the data from within each of the two randomised treatment arms that were pre-defined in the protocol for the main analyses. This was to distinguish these two arms from descriptors used for any sub-group analyses. The word had not been used in the conventional sense of combining data sets that were not pre-defined eg across different studies.

Actual population means for the treatment groups were provided, followed in each case by the table providing the results of the relevant statistical test (ie non-inferiority or superiority) and thus the statistical significance (the 'adjusted mean' listed on the analysis page was an analytical estimate only).

A Superiority claims

COMPLAINT

Pfizer stated that the leavepiece made superiority claims. Data from the STAR study had been used selectively such that the overall meaning to health professionals was misleading.

The results of the STAR study did not demonstrate superiority. From the primary endpoint, it was clear that Vesicare was non-inferior to tolterodine XL. It was not statistically accurate to make superiority claims from the secondary endpoints.

OAB was a symptom complex of four symptoms of which frequency of micturition was the most commonly reported by patients. For this symptom the STAR study had demonstrated that Vesicare was non-inferior to tolterodine XL. This was the primary endpoint.

Secondly the study also demonstrated that Vesicare was non-inferior to tolterodine XL with regard to nocturia. Urgency was an important symptom of OAB and one for which no consensus existed on how best it was quantified. In fact, considerable scientific debate still occurred on this. Finally, only one third of patients had urge urinary incontinence. The latter two symptoms were both secondary endpoints in this study and from secondary endpoints broad product superiority claims had been made.

Pfizer noted that the ICH Harmonised Tripartite Guideline on the statistical principles for clinical trials (sections 2.1.2 and 2.2.2) stated that for confirmatory trials the key hypothesis of interest was the primary objective. This was always predefined and was intended to provide firm evidence in support of claims. The primary variable should be able to provide the most clinically relevant and convincing evidence directly related to the primary objective of the trial. Clearly in the presentation of this study, this had not occurred.

It was clear that superiority claims of any type in this area had to be clearly explained in the context of a variety of symptoms that constituted OAB syndrome. Pfizer alleged that the claims were in breach of Clauses 7.2, 7.3 and 7.4.

RESPONSE

Astellas explained that this leavepiece was made available on 23 March and was primarily aimed at secondary care health professionals, although it had been used in primary care. Astellas did not consider that the data from the STAR study in the leavepiece had been used selectively such that the overall meaning to health professionals was misleading.

The primary efficacy analysis of the STAR study was to test for non-inferiority on the relatively objective measure of micturition frequency. This was demonstrated (p=0.0041). Thus it was justified to use the secondary efficacy analyses pre-specified in the protocol, provided that there was statistical

significance, to support promotional claims. As the protocol specified superiority testing for a number of parameters, where the differences met statistical significance, these could legitimately be used to support promotional claims. In the leavepiece the study design was presented diagrammatically leading on to data and claims about the product.

Within the ICS definition of OAB syndrome, urgency (with or without urge incontinence) was the defining symptom. Thus this symptom was presented in the first claim in the leavepiece. In the STAR study the reduction in urgency was statistically (p=0.0353) greater in the solifenacin treated group than in the tolterodine group, thus allowing a superiority claim. Three other pre-defined endpoints were also presented on this page, namely incontinence (graphically), percentage of patients dry and pad usage reduced.

Astellas denied breaches of Clauses 7.2, 7.3, or 7.4 of the Code.

PANEL RULING

The front cover of the four page leavepiece read 'New in overactive bladder New in flow control'. Text within a pink star read 'New data: superiority vs tolterodine XL'. The strapline beneath the product logo read 'Early results, continuing success'. 'Star – A landmark Vesicare study' in emboldened pink type face headed page two which set out the study objective and design. The study objective read 'To assess the efficacy of a flexible dose regimen of once daily Vesicare 5mg or 10mg compared to once daily tolterodine XL 4mg in patients with Overactive Bladder symptoms'. Page 3 was headed in emboldened pink typeface 'Vesicare – superior efficacy in …' beneath which comparative data for urgency episodes/24 hrs and incontinence episodes/24hrs were presented in two bar charts. Bullet points then noted that significantly more incontinent patients became dry on Vesicare compared with tolterodine XL (p=0.0059); pad usage per 24 hours was reduced in the Vesicare group compared with those on tolterodine XL (p=0.0023) whilst withdrawal rates due to adverse effects was comparable in the two groups.

The Panel considered that the leavepiece was not a fair reflection of STAR study. There was no mention anywhere of the primary finding of non-inferiority with regard to frequency of micturition. The overall impression was that Vesicare was unequivocally superior to tolterodine XL on all parameters and that was not so. The leavepiece was misleading in this regard. Breaches of Clauses 7.2, 7.3 and 7.4 were ruled.

B Encapsulation of tolterodine extended release capsule

Pfizer stated that the STAR study was conducted to a double-blind, double-dummy, randomized design. To achieve the double-dummy design Pfizer's tolterodine XL capsules were over-encapsulated into a 'blank'. The Vesicare leavepiece featured the claim 'Vesicare was superior (p=0.0059) to tolterodine XL in reducing incontinence episodes'.

COMPLAINT

The tolterodine XL capsule was over-encapsulated to produce a blinded product. In request for data to support that the two were bioequivalent Pfizer had been sent a statement from an *in vitro* dissolution study.

Pfizer noted that a bioequivalence study *was not* undertaken. It was concerned that the over-encapsulation of tolterodine XL, in the double-dummy study design, might have compromised the clinical profile of the medicine. This concern was reflected in the overall body of evidence for tolterodine XL from other studies, which appeared to demonstrate better results than that demonstrated in the STAR study.

In a table of data Pfizer summarised the results for the reduction in incontinence (52.2-69.1% vs 43.5% in the STAR study) and urge incontinence episodes (70.2-77.2% vs 39.3% in the STAR study) from other tolterodine XL studies. Whilst it acknowledged that direct comparison from different studies was not possible, it was still apparent that the efficacy of tolterodine XL for these endpoints appeared substantially different to the consistency of results in other studies ie the STAR study was inconsistent to the overall body of evidence.

With reference to the Committee for Proprietary Medicinal Products guidance (CPMP) QWP/604/96 for modified release capsules, section 2.4, Pfizer understood that bioequivalence was a requirement as tolterodine XL had been over-encapsulated and co-administered with two placebo tablets. Moreover, the only time where there was a provision for waiver of a bioequivalence study, was when the product was rapidly dissolving and/or an immediate release type preparation of a high solubility/permeability medicine. This was clearly not the case here.

In the absence of confirmation of bioequivalence, it was not possible to claim that Vesicare was more effective than tolterodine XL as the comparison was clearly invalid. Any such claims were therefore invalidated by the inadequacy of the clinical trial and were in breach of Clauses 7.2, 7.3 and 7.4 of the Code.

RESPONSE

Astellas noted that the CPMP guidance that Pfizer proposed should be applied was that which covered the use of new formulations of a marketed compound by the manufacturer. Pfizer believed that this indicated a requirement for a bioequivalence study to support the STAR study. However this guidance was not appropriate because no new formulation was involved and proprietary information for tolterodine would be required.

In order to ensure double blinding the tolterodine XL capsules used in the STAR study were disguised by the use of a simple, industry-standard, gel over-capsule; there was no backfill and tolterodine XL was not removed from the marketed capsule or subject to any other process. It would be extremely unlikely that such a procedure, used throughout the pharmaceutical industry for clinical trials, would compromise the clinical profile of tolterodine.

However, the company was diligent in testing for such a possibility, however remote.

There were no guidelines specifically for the over-encapsulation of marketed products for use in clinical trials. In the absence of specific guidance, a pragmatic approach was used in-keeping with three sets of regulatory guidance, which were for example intended for development of new formulations, modified release formulations and generics. Two were from the European Agency for the Evaluation of Medicinal Products (EMEA) and one from the Food & Drug Administration (FDA) Center for Drug Evaluation and Research. Astellas provided a table which showed that the *in vitro* tolterodine encapsulation dissolution data met the recommended conditions in the three sets of guidance.

Appendix II of EMEA guidance detailed that dissolution studies could serve several purposes, one of which was 'bioequivalence surrogate inference', such as 'to demonstrate similarity between different formulations of an active substance (variations and new, essentially similar products included) and the reference medicinal product'. Accordingly a demonstration of similarity in dissolution profiles obviated the need to conduct a bioequivalence study for a simple 'wrapping' of the marketed product to disguise its labelling and to match with a placebo. Thus in meeting the similarity factor (f_2) recommended in the three sets of guidance (of between 50 and 100) a bioequivalence study was not required.

Astellas noted that Pfizer had also claimed that the overall body of evidence for tolterodine XL from other studies appeared to demonstrate better results for the product than was demonstrated in the STAR study. Direct comparisons of separate studies were fraught with difficulties. In the simple tabulated comparison appended to Pfizer's complaint, the STAT study (Siami *et al* 2002) was an open-label trial, and therefore was not comparable to the double-blind, double-dummy design of STAR. Additionally, Pfizer had used median figures from van Kerrebroeck *et al* (2001) and Khullar *et al* (2004) to compare with a mean figure from STAR. Medians and means could not be compared.

The table of data provided by Pfizer not only misled, but was also selective, for example no mention was made that van Kerrebroeck *et al*, sponsored by Pharmacia (Pfizer), that in the tolterodine treated group the mean reduction in micturition frequency was 1.8 but if this was added to the table along with the equivalent figure from the STAR study for this variable (2.24) it would be seen that in fact a better result for tolterodine was obtained in the STAR study.

Therefore the table from Pfizer did not demonstrate that the results from the STAR study provided a question mark concerning bioequivalence.

As the data from the dissolution study accorded with regulatory guidance, a bioequivalence study was not required and therefore claims made on the results of the STAR study were valid. Thus Astella denied breaches of Clauses 7.2, 7.3, 7.4 of the Code.

PANEL RULING

The Panel noted Astellas' submission that the *in vitro* dissolution data met the recommended conditions in three sets of regulatory guidance. The Panel also noted that some of the studies referred to by Pfizer had variously used reported median reductions in daily or weekly events as opposed to the mean reduction in daily events reported in the STAR study. Although Siami *et al* had reported mean reduction in daily events, the study was open-label as opposed to the double-blind, double-dummy design of the STAR study. The Panel did not consider, on the basis of the evidence before it, that the over-encapsulation of the tolterodine XL had resulted in a decrease in its efficacy. On this basis the Panel ruled no breach of Clauses 7.2, 7.3 and 7.4 of the Code.

APPEAL BY PFIZER

Pfizer agreed that Astellas had performed *in vitro* dissolution tests according to the referenced regulatory guidelines. From these guidelines it was clear that these *in vitro* tests, without that demonstration of *in vivo* relevance, were primarily used as measure of quality control for manufacturing lot release testing. Pfizer noted in this regard the wording in those guidelines:

(i) Section 2.1.1 of the (reference QWP/604/96) guidelines for modified release capsules emphasized that 'If an *in vivo-in vitro* correlation (IVIVC) is established, the dissolution test – after proper validation – can be used as a qualifying control method with *in vivo* relevance, while in the absence of an IVIVC, the dissolution test can be used only as a quality control method'.

(ii) Section 2.1.6 clearly stated that 'By establishing a meaningful correlation between *in vitro* release characteristics and *in vivo* bioavailability parameters, the *in vitro* dissolution test can serve as a surrogate for *in vivo* behaviour and thereby confirm consistent therapeutic performance of batches from routine production'.

(iii) The approach mandated by CPMP was similar to that required by other international biopharmaceutics guidelines. For example, the Food & Drug Administration's (FDA) Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, *In Vitro* Dissolution Testing and *In Vivo* bioequivalence Documentation, (SUPAC-MR) guidance (Section III, Part C, page 12) required that all Level 3 changes to non release-controlling excipients be qualified through a single-dose bioequivalence study; the only circumstances when such study might be waived were when an IVIVC had been established.

Pfizer alleged that in the absence of an *in vivo* bioavailability study, it was not possible for Astellas to have established an IVIVC to satisfy these regulatory stipulations. In the absence of an IVIVC, it was not possible to demonstrate that the *in vitro* dissolution tests developed empirically by Astellas was indeed discriminatory for detecting possible *in vivo* differences in the bioavailability of tolterodine XL as a result of the double-blind methodology used in the STAR study ie over-encapsulation of tolterodine

XL and co-administration of two solifenacin-matching placebo tablets.

Thus Pfizer alleged that under the circumstances this was contrary to Astellas' assertion, claiming bioequivalence based on dissolution tests and was clearly inconsistent with the cited CPMP guidance and the FDA regulatory guidance.

Pfizer alleged that in the absence of this confirmation of bioequivalence, it was not possible to claim that solifenacin was more effective than tolterodine XL as the fundamental nature of this comparison was clearly invalid. Any such claims were therefore invalidated by the inadequacy of the clinical trial and were in breach of Clauses 7.2, 7.3 and 7.4.

COMMENTS FROM ASTELLAS

Astellas referred to its general comments about the STAR study above. Astellas noted that patients with OAB were entered into a single-blind, 2-week placebo run-in period then randomized to a double-blind double-dummy, 12-week active treatment period. After 4 weeks' treatment, patients were given the option of requesting a dose increase. The marketing authorization for solifenacin approved a starting dose of 5mg with an increase to 10mg if needed, whereas for tolterodine XL the approved starting dose was 4mg and no increase was approved. Thus patients requesting a dose increase who had been randomized to solifenacin received an actual dose increase (from 5mg to 2 x 5mg) whereas this was not possible for those randomized to the tolterodine group and for these patients the dose increase was 'dummied'. All patients received unlabelled medication from coded blister packs and all patients received the same dosage form throughout the study. In keeping with standard practice for comparative clinical studies every effort was made to conceal, from both the patient and the investigator, to which group the patient had been allocated. A necessary step in this process was to ensure that the medicines to be taken had a similar appearance. To conceal the identity of the marketed tolterodine capsule this was placed in a similar gel capsule, sized so that no additional filling was required: a simple, industry-standard technique for such studies.

Astellas noted that as specified in the protocol, the primary efficacy analysis was to test for non-inferiority in the change in mean number of micturitions from baseline per 24 hours. The primary efficacy analysis demonstrated that solifenacin within a flexible dose regimen was not inferior to tolterodine XL 4mg (–2.45 vs –2.24 micturitions per 24hrs respectively; p=0.0041).

Astellas alleged that Pfizer had initiated this complaint in an attempt to devalue a study which had been approved by regulatory authorities in 17 countries and independent ethics committees of 117 sites. More than 250 investigators and co-investigators participated in the study. The study had also been accepted and published in a peer-reviewed journal. These were the bodies which should correctly provide an opinion on the validity of study methods and where scientific debate should properly occur. Astellas considered that the Authority would not wish to set up as a 'higher court' in this regard. Rather it was Astellas' view that the Panel had set out in its ruling those aspects of the issue in question which were relevant to it, namely, whether the description of the design and the results of the study represented a fair and balanced view of the overall study. Astellas failed to understand the basis for Pfizer's appeal as over-encapsulation was an industry standard and this approach in the STAR study had not been questioned by the regulatory authorities, ethics committees, scientific committees or reviewers for an international journal of high standing.

Astellas noted that comparison of products was a key element of many drug development programs. Although the effectiveness of new products when measured against placebo was important, their effectiveness against existing marketed products was of even more relevance to both patients and regulatory authorities. The ability to make such comparisons was essential to the safe development of new medicines.

Astellas explained that for at least 40 years over-encapsulation had been accepted as a way to disguise comparator products in order to enable trials involving already licensed products. Gelatin capsules were a familiar and widely used dosage form in their own right, with many billions of them being taken every year.. The pharmacopoeal standards for gelatin ensured that capsules dissolve quickly and reliably. Indeed, the capsule manufacturers made capsules in special sizes designed specifically for over-encapsulation, and some licensed products were over-encapsulated tablets with differing constituents.

Industry standards for many years had been that over-encapsulation as a blinding technique was acceptable only if equivalent dissolution profiles for the un-encapsulated and the encapsulated product were found to be similar. (They were not expected to be absolutely identical because the over-capsule must take a finite time to dissolve. This was accepted.)

Astellas stated that recently, this standard had been incorporated in the draft CHMP Guideline (QWP/185491/2004) on the Requirements Relating to the Chemical and Pharmaceutical Quality Documentation Concerning Investigational Medicinal Products in Clinical Trials (drafted December 2004). Section 2.1P of the draft covered Modified Comparator Product. 2.1.P.2 'Pharmaceutical Development' stated that 'In case of solid oral dosage forms, comparative dissolution profiles of both original and modified comparator product should be provided to ensure unchanged bio-pharmaceutical properties (c.f. 'Note for Guidance on Bioavailability and Bioequivalence Testing, annex II, Dissolution Testing' for demonstrating similarity of dissolution profiles) (CHMP/EWP/QWP/1401/98, January 2002). In those cases where equivalence could not be established *in vitro*, additional clinical data to support equivalence may be necessary'. This draft Guideline showed that the authority's expectation of the 'default position' was that *in vitro* data was normally sufficient.

Astellas noted that in its appeal Pfizer had selectively quoted from various guidances designed for a very

different purpose; to ensure that there was no misunderstanding, Astellas described the intended purpose of the guidances quoted.

The first guidance quoted (CPMP/QWP/604/96) stated in the Preamble 'Pharmaceutical dosage forms may be developed in which the rate or place of release of active substance(s) has in some way been modified compared with conventional release formulations. Such modifications may have a number of objectives, but the intention of this NfG [Note for Guidance] is to cover those formulations in which the release of active substance is modified in order to maintain therapeutic activity for an extended time, to reduce toxic effects or for some other therapeutic purpose. This section II document will cover the various parts of the application for Marketing Authorization related to the quality and should be read in conjunction with section I of this NfG relating to clinical aspects'.

Astellas submitted that the guidance was therefore intended to relate to applications for marketing authorization. This guidance was therefore not appropriate to the current discussion as no new formulation was involved in the STAR study. Full adherence to this guidance in the manner suggested by Pfizer was not appropriate to the current discussion as the over-encapsulation in the STAR study did not constitute a new formulation for which regulatory approval was sought.

Pfizer had also quoted from guidance provided by the FDA which stated 'This guidance provides recommendations to Pharmaceutical sponsors of new drug applications (NDAs), abbreviated new drug applications (ANDAs), and abbreviated antibiotic drug applications (AADAs) who intend to change (1) the components or composition, (2) the site of manufacture, (3) the scale-up/scale-down of manufacture, and/or (4) the manufacturing (process and equipment) of a modified release solid oral dosage form during the postapproval period'. The introduction went on to state that 'This guidance does not affect any postapproval changes other than the ones specified'.

The EMEA guidance on Quality of Modified Release Products (CPMP/EWP/QWP/1401/98) stated that 'It is the objective of this guidance to define, for products with a systemic effect, when bioavailability or bioequivalence studies are necessary and to formulate requirements for their design, conduct, and evaluation. The possibility of using *in vitro* instead of *in vivo* studies with pharmacokinetic end points is also envisaged'. The purpose of this guidance was described in sections 4 & 5, entitled 'Applications for products containing new active substances' and 'Applications for products containing approved active substances', respectively. The latter provision was intended for those products whose formulations had changed from the reference product, for Regulatory purposes. Appendix II of this guidance detailed that dissolution studies could serve several purposes, one of which was 'Bioequivalence surrogate inference', such as 'To demonstrate similarity between different formulations of an active substance (variations and new, essentially similar products included) and the reference medicinal product'. Accordingly a demonstration of similarity in dissolution profiles obviates the need to conduct a bioequivalence study for a simple 'wrapping' of the marketed product to disguise its labelling and to match with a placebo.

Astellas submitted that other than the draft CHMP Guideline quoted above, there were no approved guidelines specifically for the over-encapsulation of marketed product for the purpose of ensuring blinding for clinical trials. Reference was made to the other guidances quoted above, only in so far as it might also have helped to inform the validation of blinded capsules using dissolution studies. It would, however, be completely inappropriate to consider that the full details of the guidance relating to marketing authorization could be translated to guidance for the purpose of clinical trials materials.

Astellas submitted that over-encapsulation of tolterodine XL in the STAR study was designed specifically to ensure absence of observer bias in the study by concealing the exact nature of the medicine from the patient and the investigator. This was standard practice in comparative clinical trials. The company took all reasonable steps to ensure that this process had not materially affected the physical characteristics of the tolterodine XL by carrying out *in vitro* dissolution studies. The methodology of these dissolution studies was based upon guidelines for dissolution tests required for regulatory purposes described in the above mentioned guidances and referred to in the draft guideline mentioned above.

Astellas explained that the tolterodine XL capsules used in the STAR study were disguised by the use of a simple, industry-standard, gel over-capsule; there was no backfill and tolterodine XL was not removed from the marketed capsule or subject to any other process. It would be extremely unlikely that such a procedure, used throughout the pharmaceutical industry for clinical trials, would compromise the clinical profile of tolterodine XL. Nevertheless, dissolution studies were performed. These confirmed that the over-encapsulated and marketed tolterodine XL capsules would be considered to meet regulatory requirements for similarity; the dissolution profiles were unaffected by pH, rotation speed, ionic strength, viscosity and surfactant providing strong evidence to support surrogate bioequivalence.

Astellas provided a table which showed that the *in vitro* tolterodine XL encapsulation data met with the recommended conditions in three sets of guidance. Astellas submitted that dissolution tests were carried out on the full pH range, which would be considered to be more than reasonable care in ensuring an absence of an effect from the over-encapsulation. The results from the *in vitro* dissolution study were also provided.

Astellas submitted thus in meeting the similarity factor (f_2) recommended in the three sets of guidance (of between 50 and 100) a bioequivalence study was not required. As the data from the dissolution study accorded with the available regulatory guidance, a bioequivalence study was not required and therefore claims made on the results of the STAR study were valid. Astellas denied a breach of Clauses 7.2, 7.3, 7.4 of the Code.

FURTHER COMMENTS FROM PFIZER

Pfizer noted that the tolterodine XL capsule was over-encapsulated to produce a blinded product in the STAR study and coadministered with two placebo tablets. It had asked Astellas for data to show that the over-encapsulated tolterodine XL used in the study was bioequivalent to the commercially available product.

An *in vitro* dissolution study had been done but not a bioequivalence study. Pfizer was concerned that the over-encapsulation might have compromised the clinical profile of tolterodine XL; the overall body of evidence for tolterodine XL from other studies appeared to demonstrate differing results than those of the STAR study.

In a table of data Pfizer summarised the results for the reduction in incontinence (52.2-69.1% vs 43.5% in the STAR study) and urge incontinence (70.2%-77.2% vs 39.3% in the STAR study) episodes from other tolterodine XL studies. Whilst it acknowledged that indirect comparisons were not always possible in this manner. Nevertheless, it was still quite apparent that the efficacy of tolterodine XL for these endpoints appeared different from the consistent results of other studies, ie the STAR study appeared to be inconsistent with the overall body of evidence.

Pfizer reiterated its complaint with regard to the over-encapsulation of tolterdine XL.

In response to Astellas' claim that Pfizer was attempting to devalue the STAR study Pfizer stated that it was actually attempting to determine the meaning of this study to ascertain its true scientific value.

Pfizer noted Astellas' submission that the validity of the STAR study should be debated by the regulatory authorities, independent ethics committees and in scientific press and not at the Authority. To a certain degree this was true, indeed, this issue has recently been bought to light in the editor's comments of a review of this study (Staskin *et al* 2005). Further, Pfizer stated that it had spoken to the principal investigator and lead author for the STAR study who had stated that he had no specific knowledge or expertise of over-encapsulation and bioequivalence. This was a consistent finding amongst experts in this area including several of the authors of the published paper.

Pfizer submitted that it was therefore entirely appropriate for it to highlight this particular issue via the Authority and to bring it to industry experts and into the scientific domain for discussion. In fact, many complaints that the Authority dealt with fell into this category ie approved studies from which claims were made were bought to the attention of the Authority by industry experts.

Pfizer acknowledged that blinding by means of over-encapsulation had been used for a long time but it was now known through bioequivalence studies that such encapsulation might affect one or more therapeutically relevant parameters of the pharmacokinetic profile of a commercial product. At Pfizer, this had been seen for active comparator drugs. It was thus now normal to qualify and confirm the bioavailability of a blinded active comparator through a properly designed and executed bioequivalence study, prior to its use in a head-to-head clinical trial.

Pfizer acknowledged that the biopharmaceutical issues it raised could be very technical in their nature and might be best appreciated by experts familiar with biopharmaceutics. It was also possible to overlook these types of issues during peer review as the reviewers might be more focused on the safety and efficacy aspects of a study.

Pfizer stated that although the regulatory guidelines did not specifically address blinding issues, the same biopharmaceutics principles that were applied to marketing applications were also valid for blinding of active comparators in trials designed for promotional claims generated from post-marketing studies.

Pfizer noted that of the three guidelines that were cited by Astellas, two were Good Manufacturing Practice (GMP) related documents. Indeed, Pfizer was confident that the product used for testing in the STAR study was GMP compliant.

Pfizer stated however, that its focus was on the biopharmaceutical aspects of double-dummy, double-blinded tolterodine XL capsule, which was a modified-release product. Important aspects of alterations of a modified release product were discussed in these guidelines also. These, as mentioned above, should also apply to blinded product's performance.

Pfizer noted that in the STAR trial, the blinded tolterodine XL capsule was not only over-encapsulated but also administered in a systematic manner along with two placebo tablets. The latter introduced not only additional inert excipients but also potentially significant amounts of release controlling polymer to the treatment. Such changes would constitute a Type II variation, which might be accepted on the basis of *in vitro* data, provided a predictable *in vitro-in vivo* correlation (IVIVC) has been demonstrated. As stated before, in the absence of an *in vivo* bioavailability study, Astellas could not have established an IVIVC. Therefore, Astellas could not claim bioequivalence based on its *in vitro* dissolution tests.

Pfizer noted Case AUTH/1222/8/01: Relpax Clinical Summary, and noted that it was assessed by the Authority. Pfizer noted that the case illustrated the effect of over-encapsulation on pharmacokinetic parameters and the importance of these clinically. In this case Pfizer had conducted head-to-head studies between eletriptan (Pfizer) and sumatriptan (GlaxoSmithKline). Sumatriptan had been over-encapsulated without backfill. Pfizer had demonstrated that the blinded over-encapsulated sumatriptan was bioequivalent to the commercially available product by a study in healthy volunteers by comparing the areas under the curve (from zero to infinity). GlaxoSmithKline however, successfully argued that bioequivalence had not been demonstrated when it mattered ie in the first 2 hours of treatment.

GlaxoSmithKline had presented data that showed the significant effect that over-encapsulation could have on the pharmacokinetic characteristics of a product.

At appeal the Appeal Board noted not only the importance of bioequivalence studies but also how important these were within a specified timeframe for an acute treatment. The Appeal Board ruled in favour of GlaxoSmithKline.

Pfizer stated that in drawing a parallel to the present case, Case AUTH/1717/6/05, the tolterodine XL capsule that was used in the STAR study was over-encapsulated in a similar way to sumatriptan. Further, it was administered with two placebo tablets that could further compromise its pharmacokinetics. And crucially, an *in vivo* bioequivalence study was not undertaken at all. The sole tests that were undertaken were *in vitro* dissolution studies.

Pfizer claimed that this case demonstrated the clear effects of encapsulation and directly supported its concerns.

APPEAL BOARD RULING

The Appeal Board dismissed the parallels drawn from a previous case, Case AUTH/1222/8/01, because in that case the medicine at issue, over-encapsulated sumatriptan, was employed for its acute effect on migraine ie there was a need for a response within the first two hours. The STAR study, however, related to the treatment of a chronic condition, tolterodine XL was a modified release product and the trial lasted 12 weeks.

The Appeal Board noted that *in vitro* dissolution tests had shown that the over-encapsulated tolterodine XL used in the STAR study was similar to the commercially available product. In such circumstances the regulatory authorities would not require *in vivo* bioequivalence testing to be done. In the absence of bioequivalence data Pfizer had speculated that the two dosage forms were not equivalent but it had no data to show that this was so.

The Appeal Board considered that on the basis of the material before it there was no evidence that the over-encapsulation of tolterodine XL had decreased its efficacy. The Appeal Board noted that gelatine capsules were designed to dissolve quickly. The Appeal Board upheld the Panel's rulings, with regard to the comparative efficacy claims in the leavepiece, of no breach of Clauses 7.2, 7.3 and 7.4 of the Code.

During the hearing Astellas disclosed that the capsules used to over-encapsulate the tolterodine XL had been manufactured by another division of Pfizer. The Appeal Board was concerned that such basic information had not previously been supplied by Astellas. The Appeal Board requested that Astellas be advised of its concern in this regard.

C Pooling of solifenacin data in the comparative claims

COMPLAINT

Pfizer explained that Vesicare was available in two doses (5mg and 10mg). The results presented in the STAR study represented the pooled results ie at the end of this study there was a treatment arm of patients who completed on solifenacin 5mg and a treatment arm that started on 5mg and titrated to 10mg. This made it difficult to determine what the actual profile was of either dosage. Not all patients would need to be titrated up to the highest dose nor was it apparent from the information presented what the benefit-risk profile was of dose titration to the maximum dose.

It was quite conceivable that the lower dosage of 5mg solifenacin would cause fewer adverse events. Hence, the pooling of the results would present a more favourable tolerability profile. Pfizer considered that the results of both the 5mg and the dose titration to 10mg tablets should be presented separately in a way in which health professionals could reliably understand the results. It was important to health professionals to know the risk-benefit profile of dose titration.

Pfizer considered this study design had a potential major flaw from which to make product claims of this type ie the results of 2 separate dosages at the end of treatment had been compared to one dose of tolterodine XL. Yet one could not know the actual profile of the differing dosages of solifenacin.

Pfizer argued that health professionals needed to know the clinical profile of both doses of solifenacin separately, in order to assess the benefit-risk profile of dose titration. It was quite conceivable that the low dose solifenacin would have lower efficacy than the data as presented. While the higher dose of solifenacin would have more adverse events. This data was important to the health professional in order to make a really informed choice that was clinically meaningful, particularly in the context of comparative product claims.

Pfizer therefore concluded that this omission in the presentation of the data and the pooling of results was selective and the basis for misleading claims.

Pfizer noted that the leavepiece made superiority claims. Pfizer stated that the data from the STAR study had been used selectively such that the overall meaning to health professionals was misleading.

Pfizer alleged breaches of Clauses 7.2, 7.3 and 7.4 of the Code.

RESPONSE

Astellas noted Pfizer's statement in its original complaint that 'the results presented in the study represent the pooled results'. This statement was scientifically incorrect. As described in the protocol, the study was designed from the beginning to look at the flexible dose regimen of solifenacin (5mg/10mg) as one treatment arm in a two treatment arm study. The results were those from a population of OAB patients randomised into two treatment groups, each group treated according to the summary of product characteristics (SPC) of each medicine. The Vesicare SPC stated that the recommended dose for solifenacin was 5mg od and health professionals could increase this dose to 10mg od if needed. The licensed dose for tolterodine XL was 4mg od. Thus in order to reflect clinical practice, for solifenacin the patients started on 5mg and in a decision made jointly by the physician and patient, a request for a dose increase could be made, and for these patients resulted in an increase to

10mg solifenacin. (The entire study was carried out under double-blind, double-dummy conditions).

Astellas stated that contrary to Pfizer's assertion, the study did provide information that was 'important to the health professional in order to make a really informed choice that is clinically meaningful' in that the design reflected the product licences and real-life practice.

Pfizer stated that 'It was important for health professionals to know the risk-benefit profile of dose titration' and that 'one could not know the actual profile of the differing dosages of solifenacin' and 'that health professionals needed to know the clinical profile of both doses of solifenacin separately, in order to assess the benefit-risk profile of dose titration'. However, the efficacy and tolerability of the two doses of solifenacin had been extensively studied in the registration trials and such information was included in the SPC. The flexible dose regimen of solifenacin was not a dose titration posology. The recommended dose was 5mg, increasing 10mg if necessary. This flexible dose regimen was reflected in the STAR study.

Astellas noted that Pfizer considered that 'this study design had a potential major flaw from which to make product claims'. This was surprising given that the regulatory authorities in 17 countries and independent ethics committees of 117 sites approved the study design and methodologies, and in excess of 250 investigators and co-investigators participated in a study designed to examine what happened in clinical practice. In light of the fact that these authorities and investigators accepted the study design it was clear that the presentation of data according to the protocol could not be viewed as being subject to 'omissions', or of being 'selective and thus misleading'.

The treatment arm of each medicine was clearly highlighted in the leavepiece in question, including:-

- The title of the study, defining the comparisons made in the study; '**S**olifenacin in a flexible dose regimen with tolterodine XL as an **a**ctive comparator in a double-blind, double-dummy, randomised overactive bladder symptom trial'.
- The study objective, also defining the comparisons made; 'To assess the efficacy of a flexible dose regimen of once daily Vesicare 5mg or 10mg (2 x 5mg) compared to once daily tolterodine XL 4mg in patients with Overactive Bladder symptoms'.
- Over half a page dedicated to a diagram of the study design, showing the two treatment arms.
- An asterix to the heading of the third page 'Vesicare – Superior efficacy in*…' pointing out that '*All figures are at endpoint for 5mg/10mg groups combined'.
- Each graph of efficacy data repeating 'Vesicare 5mg/10mg groups combined'.
- The safety/tolerability section also repeating 'Vesicare 5mg/10mg groups combined'.

Astellas therefore denied that the presentation of the flexible dose regimen of solifenacin (5mg/10mg) as one treatment arm was in breach of Clauses 7.2, 7.3 and 7.4 of the Code.

PANEL RULING

The Panel noted that the primary objective of the STAR study was to assess the efficacy of a flexible dose regimen of Vesicare 5mg or 10mg once daily compared to tolterodine XL 4mg once daily in patients with OAB. Patients could request a dose increase after four weeks of active treatment, the decision on whether to increase a patient's dose was made jointly by the investigator and patient.

The Panel noted that page 2 of the leavepiece headed 'STAR – A landmark Vesicare study' explained the study objective and referred to the flexible dose regimen of once daily Vesicare 5mg or 10mg. A graphical representation of the study design clearly set out the dosing regimen of each study arm over the 12 week study period. Two bar charts on the facing page made it sufficiently clear that the Vesicare data related to the 5/10mg od dosing regimen. Similarly, the final bullet point on that page which discussed comparable withdrawal rates for adverse events stated that the Vesicare data was for the 5mg/10mg groups combined.

The Panel noted that the Vesicare data was not pooled as alleged by Pfizer. The flexible 5mg/10mg dosing arm was one treatment arm of a two arm study. The flexible dosing arm was not a dose titration posology. According to its SPC the recommended dose of Vesicare was 5mg once daily. If needed the dose might be increased to 10mg once daily.

The Panel considered that it was sufficiently clear that the data presented in the leavepiece related to the 5mg/10mg flexible dosing arm of the study and did not consider it misleading or incapable of substantiation on this point as alleged. No breach of Clauses 7.2, 7.3 and 7.4 was ruled.

D Disparagement of tolterodine XL

COMPLAINT

Pfizer alleged that tolterodine XL was disparaged in the presentation of the STAR results and so the leavepiece was in breach of Clause 8.1.

RESPONSE

Astellas submitted that the study design of STAR was robust and widely approved as stated previously. The results of the study had been presented in a fair, balanced and factual manner, and the company denied that its materials were disparaging to Pfizer's product. On the basis of this Astellas did not consider that it was in breach of Clause 8.1 of the Code.

PANEL RULING

The Panel noted its comments and rulings above. The Panel did not consider that the leavepiece disparaged tolterodine XL as alleged. No breach of Clause 8.1 was ruled.

Complaint received **7 June 2005**

Case completed **23 December 2005**

CASE AUTH/1731/6/05

UCB PHARMA v ALK-ABELLÓ

Promotion of EpiPen

UCB Pharma complained about the promotion of EpiPen (adrenaline auto-injector) by ALK-Abelló (UK). EpiPen was indicated for immediate self administration in the emergency treatment of anaphylaxis. UCB marketed an adrenaline auto-injector as well as a number of antihistamines.

UCB stated that the homepage of the open access website www.epipen.co.uk contained the very prominent claim 'Lifeline'. From this page the reader could either click on 'Lifeline' with a warning that the site provided additional patient information to only those patients who were currently prescribed EpiPen Auto-Injectors or click on 'Epicentre' with a warning that the site was for health professionals only. However, neither route had any access control.

UCB stated that the patient information link went to a series of pages that included claims such as 'Fast-acting response to anaphylaxis', 'Buys time, saves lives' together with the EpiPen logo and product shot. A page which described the availability of twin packs of Epipen stated that these would 'bring patients clear lifesaving and practical benefits over single packs' with the 'added convenience' of 'fewer repeat prescriptions to arrange', 'only one prescription charge' and 'added reassurance'.

From the health professionals' part of the website readers could access prescribing information and download promotional materials, including a patient poster, which contained prescribing information, and a presentation discussing allergy and the use of EpiPen which did not contain prescribing information.

The prescribing information, provided by means of a link from the general website, failed to include the cost.

UCB alleged that the website promoted a prescription only medicine to the public, in breach of the Code, through lack of access control on pages directed specifically at health professionals and inclusion of inappropriate content on pages aimed at patients. The website also stated that the June edition of Allergy magazine, available in major supermarkets, would 'contain advice on … treatment including EpiPen administration'.

The Panel noted that the homepage of the website at issue explained that the Epicentre part of the site was for health professionals only and the Lifeline part of the site provided additional patient information to only those patients who were currently prescribed EpiPen Auto-Injectors. There was no password security. The Panel noted that the whole of the website was thus accessible to the public. The health professionals' section of the website included promotional claims for EpiPen; readers were able to download a presentation and a patient poster. The Panel considered that allowing the public to access this part of the website was in breach of the Code. The warnings regarding the site's intended audience were insufficient in this regard. A breach of the Code was ruled. The failure to ensure that access was restricted to health professionals meant that that part of the site promoted a prescription only medicine to the public. A breach of the Code was ruled.

The prescribing information for EpiPen which appeared on the health professionals' part of the website did not include the cost of the product. A breach of the Code was ruled.

The Panel noted that the patients' part of the website also included promotional claims for EpiPen eg 'Fast-acting response to anaphylaxis. Buys time, saves live'. The Panel considered that such claims were unbalanced and would encourage a member of the public to ask his/her own doctor for EpiPen. Breaches of the Code were ruled. Whilst this part of the site was intended for patients it was nonetheless accessible by the public. It contained promotional claims for EpiPen. Breaches of the Code were ruled.

UCB explained that the annual Allergy Show was open to the public, patients and health professionals; in 2004 only 19% of the attendees stated that they were health professionals. As such this event was primarily aimed at and attended by the public. The EpiPen website promoted a competition at the Allergy Show and stated 'Please come and visit us at Stand 91 for competitions, expert advice on all of your allergy concerns and adrenaline auto-injector instruction'. UCB stated that ALK-Abelló's stand clearly stated 'Adrenaline Auto-Injector' (but did not state EpiPen). Representatives openly discussed EpiPen with visitors, even when they were known not to be health professionals. UCB was concerned that ALK-Abelló's representatives appeared to be unaware of the Code.

A competition for attendees involved a twice-daily prize draw for an iPod. UCB alleged that this prize was in breach of the Code in terms of value, frequency, medical relevance, a lay audience and lack of *bona fide* test of skill. The competition form also included questions about 'adrenaline auto-injector' and mentioned other prescription only medicines and the indication hay fever. One question, 'Would be interested in hearing more about hay fever management?' asked for contact details. UCB alleged a breach of the Code and was concerned that ALK-Abelló was soliciting medical information requests from the public.

Everyone who completed the competition form was given a soft toy bumble-bee with an attachment which asked the recipient to 'Register on-line for an Auto-Injector Training Pack' and gave the ALK-Abelló UK website details. UCB considered that this constituted promotion of a prescription only medicine to the public in breach of the Code.

The Panel noted that patients/carers could visit ALK-Abelló's stand at the Allergy Show for expert advice on all of their allergy concerns and adrenaline auto-injector instruction. The Panel was

concerned about the arrangements but noted that it had no information before it to show that the advice had gone beyond the information allowed under the Code. The Panel also noted that ALK-Abelló had taken steps to ensure that it only gave instructions on how to use the EpiPen to those already in possession of one. On the information before it the Panel ruled no breaches of the Code.

The Panel noted the competition for patients, for which the prize was an iPod. Although patient competitions were not specifically referred to in the Code the Panel considered that the principles laid out in the Code and its supplementary information applied. The Panel considered that an iPod was neither related to the treatment of allergy nor general health. In that regard the prize was unacceptable and the Panel ruled a breach of the Code.

The Panel noted that the 'competition' was in fact a patient survey. Patients were asked general questions about their allergies including hay fever; they were asked if they would like to hear more about hay fever management. There was no indication that if a patient answered 'yes' to this question, they would be sent information about a prescription only medicine; many relevant medicines were available over the counter. On the basis of the information before it the Panel ruled no breach of the Code.

The Panel noted that everyone who completed the survey was given a small bumble-bee which directed the recipient to the EpiPen website. The Panel noted its comments and ruling above that patients accessing the website were exposed to promotional material for EpiPen. By directing patients and the public to the site ALK-Abelló had indirectly advertised EpiPen to the public. A further breach of the Code was ruled.

UCB stated that members of the public were able to request a Lifeline training pack from the website and through ALK-Abelló's stand at the Allergy Show UCB alleged that the lack of access controls for this initiative represented direct promotion to the public in breach of the Code. The pack itself contained a trainer pen, an EpiPen carrier case advising patients to carry two EpiPen auto-injectors at all times, an information leaflet on anaphylaxis, and a poster. The box described links to the EpiPen website. The poster described the use of an EpiPen but had prescribing information on the reverse and was thus not suitable for patients in breach of the Code.

The Panel noted ALK-Abelló's submission that, at the Allergy Show, it had only provided information on EpiPen to those patients already in possession of one. In that regard that Panel assumed that only patients already prescribed EpiPen would have received a Lifeline training pack. The pack described links to the EpiPen website. In addition all visitors to the stand could take part in the patient survey discussed above, and in that regard all of them would have received a bumble-bee with a message directing them to the ALK-Abelló website which was the same as the EpiPen website. The Panel noted its comments above and ruled a further breach of the Code.

The Panel noted that some patient posters had included prescribing information which was inappropriate. The posters also directed readers to the EpiPen website, which as noted above, contained promotional messages. A breach of the Code was ruled.

UCB noted that a presentation 'Epicentre anaphylaxis education' did not carry obligatory information such as prescribing information, code number or date of preparation. On the most prominent first display of the EpiPen Auto-injector brand name there was no non-proprietary name. UCB alleged a breach of the Code.

The Panel noted that the presentation did not include prescribing information a breach of the Code was ruled. In addition the non-proprietary name did not appear next to the most prominent display of the brand name, nor was there a date of preparation as required by the Code. No rulings of breaches of the Code could be ruled as UCB had not cited specific clauses, nonetheless the Panel requested that ALK-Abelló be advised that with regard to these requirements, the presentation did not comply with the Code.

UCB Pharma Ltd complained about the promotion of EpiPen (adrenaline auto-injector) by ALK-Abelló (UK) Limited. EpiPen was indicated for immediate self administration in the emergency treatment of anaphylaxis. UCB marketed an adrenaline auto-injector as well as a number of antihistamines.

A EpiPen website (www.epipen.co.uk)

COMPLAINT

UCB stated that the UK homepage www.epipen.co.uk was not password protected and so could be accessed by members of the public. The homepage contained the very prominent claim 'Lifeline'. Readers were offered two options on this page – to click on a box labelled 'Lifeline' with a warning that the site provided additional patient information to only those who were currently prescribed EpiPen Auto-Injectors or click on one labelled 'Epicentre' which contained a warning that the site was for health professionals only. However, neither route had any access control and were thus open to the public. UCB alleged breaches of Clauses 20.1 and 21.1 of the Code.

UCB stated that clicking on a patient information link took the reader to a series of pages that included the following prominent claims 'Lifeline', 'Fast-acting response to anaphylaxis', 'Buys time, saves lives' together with the EpiPen logo and product shot. UCB alleged breaches of Clauses 20.2 and 21.3 of the Code.

The page reached by clicking on 'Which EpiPen' described the availability of twin packs which would 'bring patients clear lifesaving and practical benefits over single packs' with the 'added convenience' of 'fewer repeat prescriptions to arrange', 'only one prescription charge' and 'added reassurance'. UCB alleged a further breach of Clauses 20.2 and 21.3.

Clicking on the 'Epicentre' box took the reader to the health professionals' part of the website from where they could access prescribing information and

download promotional materials. These included a patient poster, which contained prescribing information, and a presentation discussing allergy and the use of EpiPen which did not contain prescribing information, in breach of Clause 4.1 of the Code. These latter items were described below in points C and D.

The link to the prescribing information page from the general website went through to summaries of product characteristics (SPC) and prescribing information which did not contain information on cost and was therefore in breach of Clause 4.2.

UCB considered the website promoted a prescription only medicine to the public, through lack of access control on pages directed specifically at health professionals and inclusion of inappropriate content on pages aimed at patients. The website also stated that the June edition of Allergy magazine, available in major supermarkets, would 'contain advice on … treatment including EpiPen administration'. UCB alleged a breach of Clause 20.1.

RESPONSE

ALK-Abelló submitted that comprehension of the nature of anaphylaxis and the device delivering adrenaline was of essence for understanding the need for provision of education to patients, health professionals, carers, relatives and other people in the patient's near environment. Anaphylaxis was life threatening, hence the need for fast and appropriate administration of adrenaline. Currently, there were two adrenaline injectors licensed in the UK. Though both products were prescription medicines they were also medical devices and worked by different mechanisms. Therefore it was paramount that any information on how to administer the adrenaline clearly specified which pen was being described as use of generic terms in patient information would lead to mishandling and potential loss of lives. This aspect had to be borne in mind when balancing the need for provision of specific and relevant educational information and the compliance with the spirit of the Code. ALK-Abelló did not believe that there was a discrepancy between the two.

ALK-Abelló submitted that many patients suffering from an anaphylactic shock would not be able to administer their EpiPen (or other) and so it was vital that all those around them knew what to do in an emergency. For example, a child might rely on teachers or childminders and adults on work colleagues. Therefore there was a clear need for educating the patient to educate others in their proximity.

ALK-Abelló noted that the provision of educational information which was being challenged by UCB was initiated following a request from the Medicines and Healthcare products Regulatory Agency (MHRA) in July 2004. The basis for the request was a periodic safety update report on the nature of EpiPen, ie combination of medicine and device, and the potential mishandling of the device if insufficiently trained (see reference below). The request had led ALK-Abelló to develop up-to-date educational materials including the website for health professionals, patients, carers and relevant people in the immediate environment of the patient. The materials had been developed over the last twelve months and ALK-Abelló had kept the UK authorities abreast with its initiatives and intentions. Furthermore the initiatives also intended to comply with the request from the Department of Health (DoH) to provide more information and education for patients and their carers.

ALK-Abelló submitted that the need for further information to everybody involved with anaphylaxis was well-documented. Hayman *et al* (2003) reported that 98% of GPs did not know how to operate the adrenaline devices which they had prescribed, none of them spent time educating their patients, 80% left that to the practice staff and the remaining 20% did not provide any training. The same study assessed secondary care patients' knowledge of how and when to use the device prescribed to them. Considering that anaphylaxis could be deadly the numbers were shockingly low as only 35% of parents could assist their at-risk child (<8 years) and only 14% of adult patients knew how to administer the adrenaline prescribed to them. These findings mirrored those of a number of similar studies.

ALK-Abelló submitted that the EpiPen website was developed to provide information to patients and carers and be a source of educational materials. The company had not intended to promote EpiPen to the public and the site was not meant for the public. The UK homepage was explicit in providing warnings to both patients and health professionals.

ALK-Abelló submitted that the website was clearly intended for health professionals and for patients who had already been prescribed an EpiPen. The specific warnings were shown twice before the site was accessed and anyone without proper entitlement would deliberately and wrongfully be accessing the website. There was absolutely no intention to advertise either directly to the public or to provide patients with access to promotional materials.

ALK-Abelló submitted that the website had been developed to provide health professionals and patients with sound and up-to-date information on anaphylaxis in response to the MHRA's request to make EpiPen training materials and information readily accessible to health professional and carers and so reduce any mishandling of the product. Discussions between ALK-Abelló and the MHRA dated back to July 2004, and on request ALK-Abelló had provided the agency with a status on this initiative in March 2005. Furthermore, the website was also intended to comply with the request from the DoH to provide more information and education for patients and their carers.

Nevertheless, ALK-Abelló submitted that through inter-company dialogue with UCB and in light of the concerns raised, it had agreed in 2005 to review the website. It was therefore disappointing that UCB Pharma had referred the matter to the Authority.

ALK-Abelló noted that access control of the health professional part of the site had been debated but was not feasible as EpiPen advice and anaphylaxis education were provided by school nurses, paramedics, practice nurses and secretaries,

pharmacists as well as GPs (even though the above numbers had not supported any involvement). ALK-Abelló submitted that whilst password protection was relatively straightforward for medically qualified personnel (requiring them to enter their GMC number), it was far from obvious as to how it could restrict the site to other health professionals, especially nurses, paramedics, pharmacists and pharmacy assistants, as they might not have an equivalent membership number. ALK-Abelló was currently investigating a solution to this issue that, from a review of other health websites, appeared to be a common problem; however restricting the sites to doctors, would fail the objective.

Moreover, those seeking information who were deterred from accessing the UK information normally went to www.epipen.com which was the site suggested by the Google and Yahoo search engines when typing in 'EpiPen'. This US site was freely accessible and provided US information of a strong promotional nature, information in discordance with the UK advice for this particular device. The Anaphylaxis Campaign Hotline as well as ALK-Abelló's own records of telephone queries confirmed that the US information gave rise to significant and dangerous confusion. It was therefore considered to be of essence to provide those in the UK with an appropriate and correct source of information rather than deter them.

ALK-Abelló submitted that since the website was launched July 2004, thousands of verified health professionals had requested its health professional training pack which supported the conclusion of the above mentioned study: there was a clear need for training in allergy and anaphylaxis disease management among health professionals including nurses, pharmacists and paramedics in the UK. ALK-Abelló noted that less than 20 people who were not health professionals had requested material including the training pack which suggested that patients were using the correct 'Lifeline' section of the website. Since there was more than adequate information on the patients' part of the website there was no motivation for them to visit the health part of the site, a situation which had been discussed with the MHRA.

ALK-Abelló accepted that the claim 'Fast-acting response to anaphylaxis, Buys time, saves lives' should not be accessible by patients, however it did not accept that the claim was neither factual nor presented in a balanced way as it was obvious that a fast response (well documented with adrenaline administered in this way) would buy time and save lives. Furthermore, no comparative claims were made. Clause 20.2 also stated 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 home page of the website clearly stated that the website provided additional information to only those patients currently prescribed an EpiPen Auto-Injector. Therefore, as a prescription should already have been issued, the statement was clearly not intended to encourage members of the public to ask their doctors to prescribe EpiPen. It was intended to reassure patients about the medicine they had been prescribed. Nevertheless, to avoid any dispute the claim would be removed. Additionally the wording in this section had been amended to remove any claims that could be perceived to be promotional.

ALK-Abelló submitted that the claim 'Which EpiPen' – availability of twin packs 'bringing patients clear lifesaving and practical benefits over single packs' was only intended for health professionals and only appeared in the section of the website for health professionals. There was an identical heading in the patients' part of the website where, quite intentionally, such claims had not been made. The patients 'Which EpiPen' section focused on how to use the EpiPen, dosage and administration. ALK-Abelló therefore did not accept a breach of Clauses 20.2 and 21.3.

ALK-Abelló noted the complaint regarding the 'Epicentre' box – prescribing information and downloadable promotional materials, including a patient poster', and submitted that the PowerPoint slides illustrated quite clearly the intended educational nature of the content of this presentation. However, as the presentation had mentioned EpiPen, ALK-Abelló accepted that it should have contained prescribing information. The link to the prescribing information page from the SPC should also have contained information on cost. Both these points were now being addressed to ensure compliance with Clauses 4.1 and 4.2.

Taken as a whole, ALK-Abelló rejected the allegations that the website clearly and intentionally promoted a prescription only medicine to members of the public. The website clearly stated the intentions of the two respective sections, namely to provide health professionals and patients already prescribed EpiPen, with up-to-date and sound information on anaphylaxis.

ALK-Abelló stated that it was factually correct that one of the articles (which was not written by ALK-Abelló) in the June edition of 'Allergy' magazine contained advice on avoiding bee and wasp stings and treatment, including EpiPen administration. Again this was intended as information solely for patients for whom a prescribing decision had already been taken and so ALK-Abelló did not accept a breach of Clause 20.1.

PANEL RULING

The Panel accepted ALK-Abelló's submission that understanding the nature of anaphylaxis and the use of the device delivering adrenaline was essential for patients, carers, relatives and others. As the two adrenaline devices available in the UK worked by different mechanisms it was important that information for patients, carers, etc specified which device it related to. The provision of information needed to comply with the Code.

The Panel noted that Clause 21.3 of the Code required that information about prescription only medicines which was made available on the Internet and which could be accessed by the general public, had to comply with Clause 20.2 of the Code ie it must be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be

misleading with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their doctors to prescribe a specific medicine. Clause 21.1 of the Code required access to promotional material on the Internet for prescription only medicines to be limited to health professionals and appropriate administrative staff.

The Panel noted that the homepage, beneath the headings 'Warning', explained that the Epicentre part of the site was for health professionals only and the Lifeline part of the site provided additional patient information to only those patients who were currently prescribed EpiPen Auto-Injectors. There was no password security. The Panel noted that the whole of the website www.epipen.co.uk was thus accessible to the general public, including that part of it which was for health professionals only. The health professionals' section of the website included promotional claims for EpiPen; readers were able to download a presentation and a patient poster. The Panel considered that allowing the general public to access this part of the website was in breach of Clause 21.1 of the Code. The warnings regarding the site's intended audience were insufficient in this regard. A breach of Clause 21.1 was ruled. The failure to ensure that access was restricted to health professionals meant that that part of the site promoted a prescription only medicine to the general public. A breach of Clause 20.1 was ruled.

The prescribing information for EpiPen which appeared on the health professionals' part of the website did not include the cost of the product. In this regard UCB had alleged a breach of Clause 4.2 of the Code. Clause 4.2, however listed the component parts of the prescribing information. Clause 4.1 required the information listed in Clause 4.2 to be provided; failure to do so would thus be a breach of this clause and not of Clause 4.2. Failure to include details of cost in the prescribing information meant that ALK-Abelló had not complied with Clause 4.1. A breach of Clause 4.1 was ruled.

With regard to the patients' part of the website the Panel noted that it too included promotional claims for EpiPen eg 'Fast-acting response to anaphylaxis. Buys time, saves live'. The Panel considered that such claims were unbalanced and such that they would encourage a member of the public to ask his/her own doctor for EpiPen. Breaches of Clauses 20.2 and 21.3 were ruled. Whilst this part of the site was intended for patients it was nonetheless accessible by the general public. It contained promotional claims for EpiPen contrary to Clause 20.1. A breach of that clause was ruled accordingly. Consequently a breach of Clause 21.1 was also ruled.

During its consideration of this matter, the Panel noted ALK-Abelló's submission with regard to the practicalities of password protecting a website designed for various health professionals and the use of membership numbers. In the Panel's view there were other ways to password protect a website. Whatever system was used companies must ensure that if promotional material was made available on the Internet then it was accessible to health professionals only via a secure closed system.

B Promotion to the general public at the Allergy Show, Olympia 17-19 June to 2005

COMPLAINT

UCB explained that the annual Allergy Show was open to the public, patients and health professionals; in 2004 only 19% of the attendees identified themselves as health professionals. As such this event was primarily aimed at and attended by the public.

The EpiPen website promoted a competition at the Allergy Show and stated 'Please come and visit us at **Stand 91** for competitions, expert advice on all of your allergy concerns and adrenaline auto-injector instruction'. UCB alleged breaches of Clauses 20.1 and 20.3 of the Code.

UCB stated that ALK-Abelló had a promotional stand at the Allergy Show that clearly stated "Adrenaline Auto-Injector" (but did not state EpiPen). Representatives openly discussed EpiPen with visitors to the stand, even when they were known not to be health professionals. UCB was concerned that ALK-Abelló's representatives appeared to be unaware of the Code governing interaction with the public.

A competition for attendees involved a twice-daily prize draw for an iPod. UCB alleged that this prize was in breach of Clause 18.2 of the Code in terms of value, frequency, medical relevance, a lay audience and lack of *bona fide* test of skill. The competition form also included questions about 'adrenaline auto-injector' and mentioned other prescription only medicines and the indication hay fever, namely Beconase (nasal steroid), prednisolone (oral steroid). Question 12 asked if the participant 'Would be interested in hearing more about hay fever management?' and for contact details. UCB alleged a breach of Clause 20.3 and was concerned that ALK-Abelló appeared to be soliciting medical information requests from the public.

A prize for completion of the competition form was a soft toy bumble-bee with an attachment which asked the recipient to 'Register on-line for an Auto-Injector Training Pack' and gave the ALK-Abelló UK website details. UCB considered that this constituted promotion of a prescription only medicine to the public in breach of Clause 20.1.

RESPONSE

ALK-Abelló agreed that the Allergy Show was primarily aimed at and attended by the public, especially patients with allergies, parents or children with allergies and also health professionals that treated them. For this reason, ALK-Abelló wanted to provide expert instruction to patients about the administration of EpiPen but strictly only to those already prescribed an EpiPen and who were in possession of their EpiPen when visiting the stand. The company had refused to provide this advice and instruction to two patients carrying the UCB branded adrenaline auto-injector. Prior to implementing this approach, ALK-Abelló sought advice and guidance from the MHRA that this was acceptable practice and could not be construed as promoting a medicine direct to patients. The MHRA concurred with this view. Consequently a nurse was present on the stand

for one afternoon to provide instruction and advice on administration to those patients carrying their EpiPen. ALK-Abelló therefore rejected the allegation of a breach of Clause 20.1 on this point. Furthermore, ALK-Abelló submitted that its representatives only discussed EpiPen with patients and their attending relatives who had provided evidence that they were in possession of and had been prescribed the product. At no point did any of ALK-Abelló staff use the term EpiPen unless directly asked about EpiPen.

ALK-Abelló submitted that regarding Clause 20.3, requests for information or advice on personal medical matters, it had deliberately avoided providing consumers/patients with any prescribing information. No information on allergies, such as hay fever or asthma, was provided that was not in the public domain. Furthermore, ALK-Abelló stated that it sponsored neither doctors nor health professionals on the stand advising on 'personal medical matters', it therefore refuted the allegation of a breach of Clause 20.3.

ALK-Abelló stated that the 12 questions of the competition were general allergy questions and neither overtly nor covertly promoted EpiPen. The competition was clearly aimed at patients not health professionals so the prize offered did not need to comply with Clause 18.2 of the Code regarding inexpensive gifts with a cost to the donor company of £6 excluding VAT. The competition was neither designed to test skill (of patients not health professionals) nor be medically relevant (to patients). That said, an iPod was of considerable relevance and value to patients. ALK-Abelló accepted this value was greater than £6 but less than £100 as was the limit of competitions and as the competition was only open to patients not health professionals it rejected a breach of Clause 18.2.

ALK-Abelló noted UCB's other allegations about the competition and it defended its decision to include the brand names of other prescription only medicines as patients, in their response to question 10, remembered the names of the OTC medicines they were taking such as Piriton and Beconase and not their generic names (chlorphenamine maleate and beclometasone dipropionate!).

ALK-Abelló noted that question 12 was a general question regarding interest in hearing more about hay fever management and could surely not be construed as requesting information on personal medical matters. ALK-Abelló rejected any breach of Clause 20.3.

Registering on line for an Auto-Injector training pack was intended to be an educational service to patients for whom a prescribing decision had already been taken not as a way to promote EpiPen to patients via the website. In order to assure this was restricted to patients only, a valid EpiPen expiry date had to be entered before proceeding and a pack would be shipped.

PANEL RULING

The Panel noted that patients/carers could visit the ALK-Abelló stand at the Allergy show for expert advice on all of their allergy concerns and adrenaline auto-injector instruction. Clause 20.3 of the Code prohibited the provision of information or advice on personal medical matters to individual members of public. The intention behind this prohibition was to ensure that companies did not intervene in the patient/doctor relationship by offering advice or information which should be given by the patient's own doctor. However companies could give patients some information on their medicines provided that it complied with the requirements of Clauses 20.1 and 20.2 and did not impinge on the principle behind Clause 20.3.

The Panel was concerned about the arrangements but noted that it had no information before it to show that the 'expert advice on all of your allergy concerns' as offered by ALK-Abelló, had gone beyond the information allowed under the Code. The Panel also noted that the company had taken steps to ensure that it only gave instructions on how to use the EpiPen to those already in possession of one. On the information before it the Panel ruled no breaches of Clauses of 20.1 and 20.3.

Clause 18.2 of the Code allowed the provision of gifts in the form or promotional aids and prizes. The supplementary information to Clause 18.2, gifts to or for use by patients stated that such items should meet the relevant principles set out in Clause 18.2 ie that they should be inexpensive and related to either the condition under treatment or general health. The provisions of Clause 18.2 applied to the provision of competition prizes. Prizes of a higher value than would ordinarily be acceptable for a promotional aid were acceptable where, *inter alia*, the competition was a serious one and the prizes few in number. The maximum acceptable cost to the donor of a prize in a promotional competition was £100, excluding VAT.

The Panel noted that ALK-Abelló had run a competition for patients, for which the prize was an iPod. Although patient competitions were not specifically referred to in the Code the Panel considered that the principles laid out in Clause 18.2 and its supplementary information applied. In that regard the Panel noted that the introduction to the Code referred to companies abiding by both the spirit and the letter of the Code. The Panel considered that an iPod was related to neither the treatment of allergy nor general health. In that regard the prize was unacceptable and the Panel ruled a breach of Clause 18.1 of the Code.

The Panel noted that the 'competition' was in fact a patient survey regarding allergy. Patients were asked general questions about their allergies including hay fever. Patients were asked if they would like to hear more about hay fever management. There was no indication that if a patient answered 'yes' to this question, they would be sent information about a prescription only medicine; many medicines used to treat hay fever were available over the counter. On the basis of the information before it the Panel ruled no breach of Clause 20.3 of the Code.

The Panel noted that everyone who completed the survey was given a small bumble-bee which directed the recipient to the EpiPen website. The Panel noted

comments and its ruling at point A above that patients accessing the website were exposed to promotional material for EpiPen. By directing patients and members of the public to the site ALK-Abelló had indirectly advertised EpiPen to the public. A further breach of Clause 20.1 was ruled.

C Promotional poster in a 'Lifeline' training pack

COMPLAINT

UCB stated that members of the public were able to request a Lifeline training pack from the EpiPen website due to the reasons outlined in point A above and also due to the competition and information given to the public in point B above. Whilst UCB welcomed the further provision of product information to those patients already prescribed EpiPen (via a health practitioner), due to the lack of controls of access this initiative represented direct promotion to the public. UCB alleged a breach of Clause 20.1 of the Code.

The pack itself contained a trainer pen, an EpiPen carrier case advising patients to carry two EpiPen auto-injectors at all times, an information leaflet on anaphylaxis, and a poster. The box described links to www.epipen.co.uk.

The poster (ref C56720/0904) described the use of an EpiPen but had prescribing information on the reverse and was thus not suitable for patients. UCB alleged a breach of Clause 20.2.

RESPONSE

ALK-Abelló stated that it was glad that UCB had welcomed the further provision of product information to those patients already prescribed EpiPen, as already stated that was clearly its intent. ALK-Abelló rejected that this initiative had constituted overt and wilful direct promotion to the public but it accepted that a limited number of a poster intended for informing patients should not have carried prescribing information, which had been removed. However, ALK-Abelló denied that this was included deliberately to encourage members of the public to ask their doctors to prescribe EpiPen and therefore did not accept a breach of Clause 20.2. This was known to UCB as the following statement was included in a letter to the company dated 23 June 2005: 'By mistake a few Lifeline packs may have included a poster with prescribing information as our external mailing company has admitted to mixing the various poster versions. This is only the case for approximately 50 packs, and the situation has now been rectified.'

PANEL RULING

The Panel noted ALK-Abelló's submission at point B above that, at the Allergy show, it only provided information on EpiPen to those patients already in possession of one. In that regard that Panel assumed that only patients already prescribed EpiPen would have received a Lifeline training pack. The pack described links to the EpiPen website. In addition all visitors to the stand could take part in the patient survey discussed at Point B above, and in that regard all of them would have received a bumble-bee with a message directing them to the ALK-Abelló website which was the same as the EpiPen website. The Panel noted its comments above and ruled a further breach of Clause 20.1 of the Code.

The Panel noted that some patient posters had included prescribing information which was inappropriate. The posters also directed readers to the EpiPen website, which as noted above, contained promotional messages. A breach of Clause 20.2 was ruled.

D 'Epicentre anaphylaxis education' PowerPoint presentation

COMPLAINT

UCB noted that this presentation (aimed at health professionals but available to the public for reasons described in point A above) did not carry obligatory information such as prescribing information, code number or date of preparation. On the most prominent first display (contents page) of the EpiPen Auto-injector brand name there was no associated non-proprietary name in breach of Clause 4.1 of the Code.

RESPONSE

ALK-Abelló confirmed that this presentation was aimed at health professionals only, not the general public, and it accepted that it should have carried obligatory information such as prescribing information, code number or date of preparation. ALK-Abelló undertook to implement these additions, and accepted to include on the most prominent display (contents page) of the EpiPen Auto-injector brand name, the associated non-proprietary name in order to ensure compliance with Clause 4.1 of the Code.

In summary, ALK-Abelló submitted that it had tried to comprehensively address all of the points and allegations raised by UCB. ALK-Abelló had acted in good faith and with the primary interest and intention of providing quality education and information to health professionals and their patients. ALK-Abelló rejected the allegations made of any wilful intention to promote its product directly to patients or to breach the Code.

PANEL RULING

The Panel noted that the PowerPoint presentation did not include prescribing information as required by the Clause 4.1 of the Code. A breach of that clause was ruled. In addition the non-proprietary name did not appear next to the most prominent display of the brand name as required by Clause 4.3 of the Code nor was there a date of preparation as required by Clause 4.9. No rulings of breaches of these further clauses could be ruled as UCB had not cited them, nonetheless the Panel requested that ALK-Abelló be advised that with regard to these requirements, the PowerPoint presentation did not comply with the Code.

Complaint received	**27 June 2005**
Case completed	**20 October 2005**

CASE AUTH/1737/7/05

ANONYMOUS MEDICAL REPRESENTATIVE v ASTRAZENECA

Call rates for representatives

An anonymous medical representative from AstraZeneca complained about the company's policies in relation to call frequency.

The complainant noted that following a number of complaints against AstraZeneca, senior managers had recently addressed the field force regarding its responsibilities under the Code. The complainant was dismayed to hear a succession of statements claiming that the management team had failed to be 'clear' on their directions to sales staff and had 'made assumptions' – thereby attempting to distance themselves from any complaint. This was questionable. The complainant noted call frequency targets. The complainant stated that at a national sales conference a senior executive had deliberately and seriously told the audience that if they were not being thrown out of at least one surgery a month then they were not doing their job. In a subsequent address, the executive referred back to his comment adding that he was aware that many of the field force had been unhappy at the implications but he gave no retraction or apology for it. The complainant considered that such a statement was indicative of the everyday approach taken by AstraZeneca management, reflected in appraisal documentation and in incentive schemes.

The Panel noted the complainant's very general comments about the company's approach to the field force, incentive schemes and call rates but did not consider that it had a specific allegation in this regard.

The Panel noted the complainant's allegation that a senior executive advised the audience at a national sales conference that if they were not thrown out of a surgery at least once a month then they were not doing their job. AstraZeneca conceded that a senior executive had made a closely similar remark at two divisional meetings in 2002. The Panel had inferred from the complaint that the statement at issue might have been made recently; the complainant described him/herself as dismayed by the remark and stated that senior management had recently addressed the field force on its responsibilities under the Code. The position was thus unclear. It was not possible to seek further information from the complainant who was anonymous.

The Panel noted AstraZeneca's submission that the statement at issue made by the senior executive was part of a personal anecdote during a motivational presentation to encourage a more dynamic approach. Some of those who had been in the audience were concerned that the statement could be misinterpreted by inexperienced representatives whilst others described it as challenging and assertive. The Panel considered that the executive's comments were inappropriate and likely to lead to a breach of the Code. High standards had not been maintained. Breaches of the Code were ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was used to indicate particular censure.

An anonymous medical representative from AstraZeneca UK Limited complained about the company's policies in relation to call frequency.

COMPLAINT

The complainant stated that a number of complaints had been made against AstraZeneca and as a result, senior management had recently addressed the field force regarding its responsibilities under the Code.

The complainant was dismayed to hear a succession of statements claiming that the management team had failed to be 'clear' on their directions to sales staff and had 'made assumptions' – thereby attempting to distance themselves from any complaint. This was questionable. The complainant drew attention to call frequency targets. A senior executive addressed a national sales conference on doctor contact requirements and told the audience that if they were not being thrown out of at least one surgery a month then they were not doing their job. The statement was delivered without humour and was not a joke; it was deliberate, serious and aggressively made. In a subsequent address, the executive referred back to his comment adding that he was aware that many of the field force had been unhappy at the implications. There was no retraction, no apology – simply a reminder delivered with a smile.

The complainant considered that the statement was indicative of the everyday approach taken by AstraZeneca management, reflected in appraisal documentation and in incentive schemes. The complainant suggested that a review of individual appraisal reports would reveal how 'poor performers' with regard to call rates were penalised.

More importantly, the executive's actions clearly demonstrated that the field force had been encouraged to inconvenience the medical profession to such an extent that they were ejected and barred from premises. Representatives did not seek confrontation and it was a credit to them that they had continued to develop positive relationships with their customers in the face of such aggressive management direction. Responsibility and therefore accountability must rest with those who created such an unpleasant working environment for the field force. Instead they sought to lay blame on those who were too afraid to challenge them.

The Authority should consider how such a direction would impact upon the reputation of the industry as a whole. Was this the kind of leadership that was to be condoned, excused and rewarded?

The complainant was sure that the executive would either deny his comments or claim that they were not

seriously made. Not so. Many of those present had recently recalled the event – it had had lasting impact. Should the Authority wish to canvass their recollections then email or postal assessment would not provide sufficient anonymity and the 'fear culture' that ran throughout AstraZeneca would dominate. This fear culture also prevented the complainant from revealing his/her identity. Reprisals would be severe and covert. However, representatives had been asked by the management team to report any alleged breaches of the Code made either by themselves or colleagues. The complainant trusted therefore that the Authority would investigate this matter in full and require AstraZeneca to communicate both the nature of the complaint and the Authority's findings to all sales and marketing staff.

When writing to AstraZeneca, the Authority asked it to respond in relation to Clauses 2, 9.1 and 15.9 of the Code.

RESPONSE

AstraZeneca stated that it had found it difficult to investigate this complaint because of the elapsed time and because it appeared to be a general statement of an individual's dissatisfaction with the leadership and management of the company. It also appeared to relate in part to the remedial action that AstraZeneca had taken to address some of the issues raised in Case AUTH/1714/5/05.

With no specific date or description of where and when the meeting at which the alleged statement was made took place, AstraZeneca thought that the complainant might be referring to two meetings in September 2002. The company was surprised that one of its employees had felt compelled to complain nearly three years after the alleged incident. It was also extremely disappointed that such a complaint had been made since the company had recently put in place very thorough measures to ensure that call frequency, and all other activities, complied with the Code.

AstraZeneca stated that its full and thorough investigation into all aspects of the complaint included:

- Asking the executive for his recollections of making the alleged statement
- Interviewing attendees who had been at presentations made to the salesforce by him
- Asking relevant second line sales managers if members of the salesforce had been ejected or barred from premises
- Reviewing market research on customers' views of AstraZeneca representatives
- Reviewing all accessible records of complaints received by the company since 2002
- Collecting and reviewing salesforce briefing materials relating to coverage and frequency and call rates
- Reviewing the incentive scheme; and
- Reviewing the disciplinary and grievance records to see if this revealed or could have driven inappropriate behaviour relating to the complainant's allegations.

AstraZeneca stated that the definitions of call rate and frequency were:

Call rate: the number of calls made by a representative against specified customer groups in a given period of time. A call rate of 4 per day would mean that a representative had seen 4 of their customers in that day.

Call frequency: the number of times a particular target doctor was required to be seen over a given period of time. A call frequency of 4 per quarter for Crestor would mean that the target was for this doctor to be detailed on Crestor 4 times in one quarter by a team of representatives (not any one individual representative).

1 Allegation that the executive specifically condoned breaching the Code in presentations given by him in 2002

AstraZeneca noted that the complainant had alleged that the speaker encouraged the salesforce to behave in a manner that would get them ejected from surgeries on a regular basis. In effect, that he had actually condoned breaching the Code. Such behaviour would never be tolerated by the business either now or at the time the meetings took place. Any damage to relationships with customers was directly against the interests of the company and would result in diminished opportunities and sales growth.

The executive did not recall using the specific words quoted by the complainant. However, he thought that he might have used language along the lines of 'being thrown out of a surgery' as part of a personal anecdote at a sales meeting in 2002, in the context of a presentation on the performance of AstraZeneca's primary care sales force. The presentation showed that AstraZeneca call rates were below the industry average. It was his belief that AstraZeneca brands had advantages over competitor brands and therefore the sales force needed to challenge customers more on their prescribing behaviour. In this presentation he emphasized that AstraZeneca was not a company just chasing calls and that the quality of the call was very important. This presentation was intended to be motivational and to encourage a more dynamic approach.

Subsequent interviews with other AstraZeneca staff identified that there were three divisional primary care sales meetings held in September 2002. Out of the 15 people interviewed, 9 (who had attended the meetings) recalled that a statement had been made by the executive at two of the three meetings. None of the interviewees could recall the precise words used but some referred to language similar to that recalled by him. From the interviews there was no evidence that the statement made by him was repeated at any other meeting since September 2002. The statement as alleged by the complainant, or anything similar, did not appear in his speaker notes or slides and the presentations were not videoed. The presentation was not certified as it was an overview presentation.

Four of the interviewees were surprised at his choice of words and concerned that they could be misinterpreted by inexperienced representatives but none interpreted the statement as a directive nor did they believe they were being asked to break the Code. Most of those who remembered the statement thought it was a motivational call to illustrate the need for the sales force to improve its performance compared to the industry average. None of the interviewees described the statement as being 'deliberate, serious and aggressively made', rather the presentation was described as assertive and challenging in line with that expected from the individual in question.

AstraZeneca stated that interviews with second line sales managers (15/20) revealed no reports of AstraZeneca representatives being ejected and/or barred from premises as alleged by the complainant. AstraZeneca had no records in its central offices of any such complaint being lodged against it. AstraZeneca would treat such a complaint very seriously.

2 Allegations that there was an everyday approach taken by AstraZeneca management that condoned breaching the Code either historically or currently

AstraZeneca stated that it, like most other pharmaceutical companies, made available a non contractual incentive scheme for its field force. The incentive offered was in line with that offered by major competitors. AstraZeneca gave details of the scheme and noted that pursuant to Case AUTH/1714/5/05, it had changed it to ensure it did not incentivise call frequency. Representatives' incentive reward had never (in the last three years) been significantly influenced by call rate achievement. The opposite was actually true with the vast majority being driven by sales and market share achievement. Sales representatives were also part of Inspire, an overall performance management programme, as were all AstraZeneca UK marketing company staff. Inspire linked objective setting, performance assessment, coaching and feedback and reward processes. The existence and structure of Inspire were widely publicised on the company intranet, via staff communications and by management cascade. In 2004 the Inspire programme determined representative performance ratings against a range of contributory factors. Sales versus target contributed 60% of the overall rating; In-call performance contributed 20%; focus on delivery 10% and attitude 10%. All ratings were subject to peer and line manager validation. Focus on delivery (10% of the overall rating) included a range of measures including activity versus target, coverage and frequency versus target and days in the field; activity and coverage and frequency were thus two relatively insignificant components. Activity and coverage and frequency targets were set as inspirational, stretch targets. It was very rare for there to be disciplinary discussions around call activity rates with individuals and to AstraZeneca's knowledge there had not been any disciplinary discussions around frequency of calls. AstraZeneca noted that the Inspire briefings had a statement that *'calls must adhere to ABPI guidelines'*. The only exception to this was the Inspire briefing to the psychiatry sales team where the statement was inadvertently omitted.

3 The working environment and culture within AstraZeneca

With regard to the allegations relating to working conditions and fear culture, AstraZeneca stated that it placed great importance on working conditions and environment and noted that it had received a number of independent accolades and awards attesting to the company being good to work for and with its representatives being seen as professional and successful.

AstraZeneca promoted a culture of open communication and a number of mechanisms and structures were in place to enable employees to raise issues and concerns and for ensuring this was done fairly.

In addition a compliance officer, appointed in March 2005, reported into the legal function with the primary objective of ensuring business compliance and not business performance. Employees could seek advice or raise issues on a confidential basis with the compliance officer; the compliance hotline, a confidential telephone line, could be used to report any compliance issues.

Employees had been happy to openly submit questions on the Code at meetings and training sessions. These questions had been addressed via a company intranet site. Recent face-to-face training workshops had also encouraged all employees to ask questions and highlight any areas that they did not understand or had concerns about. This desire for openness was acknowledged in the complaint although it had clearly been misinterpreted – 'However, the representatives had been asked by the management team to report any alleged breaches of the Code made either by themselves or colleagues'.

The result of all these communications had been the creation of an extensive list of questions and answers which had been posted onto the corporate governance website as a reference document for all employees.

In addition to all of these UK marketing company initiatives, the global organisation also sought to create an atmosphere of open and transparent dialogue where compliance was always the top priority for each individual. The group's latest annual report and also the company's Code of Conduct, which was provided to every employee stated: 'Nothing – not the need to meet targets, or direct orders from a superior – should ever compromise our commitment to honesty and integrity'.

AstraZeneca stated that it had gone to great lengths to ensure that all of its activities complied with the Code and had communicated this widely. A communications programme was put together with input from senior managers including those from the salesforce. Details were provided.

The purpose and objective of the programme was for the UK directors and other senior managers to consult in an open and transparent way, to take feedback and

to present on historical, current and future issues. All of these activities underpinned the form of undertaking for Case AUTH/1714/5/05. The feedback on the programme had been overwhelmingly positive. AstraZeneca therefore found it very difficult to reconcile this with the content and general tone of the complaint.

AstraZeneca submitted that following the receipt of the Panel's ruling in Case AUTH/1714/5/05, it had briefed the whole organisation regarding the withdrawal of all frequency targets for the remainder of 2005, while the issues raised therein were addressed. In addition it withdrew all coverage and frequency based incentive schemes.

Conclusion

AstraZeneca could find no hard evidence that the executive concerned made the alleged statement, but it did receive some recollections from him and other employees of a statement made almost three years ago. It was possible that this statement could have been misinterpreted by some individuals, but AstraZeneca could not find any evidence that this was the case. The only complaint it had received about the alleged statement was from this complainant, almost three years after the alleged event. There was no evidence that the statement was in any way directive and it was not part of any recognized formal briefing or culture. In addition there was no evidence that representatives either (a) changed their behaviours to breach the Code or (b) were ever 'thrown out of surgeries' as a result of such a statement. AstraZeneca therefore denied any breach of Clauses 2, 9.1 and 15.9.

AstraZeneca stated that it took corporate governance and compliance with the Code very seriously and had continually briefed and trained personnel on the Code requirements, including yearly updates and training on the introductory training course for new starters.

FURTHER COMMENTS FROM ASTRAZENECA

In response to a request for all relevant briefing materials, AstraZeneca explained that it had included all relevant briefing materials with its original response. AstraZeneca provided a detailed description of the AstraZeneca sales organisation, the definition and communication of activity targets and materials used to support communication of representative activity targets.

PANEL RULING

The Panel noted the complainant's allegation that a senior executive told the audience at a national sales conference that if they were not thrown out of a surgery at least once a month then they were not doing their job. AstraZeneca conceded that a closely similar remark had been made by one of the senior executives at two divisional meetings in 2002. The Panel had inferred from the complaint that the statement at issue might have been made recently; the complainant described him/herself as dismayed by the remark and stated that senior management had recently addressed the field force on its responsibilities under the Code. The position was thus unclear. It was not possible to seek further information from the complainant who was anonymous.

The Panel noted that the complainant had made very general comments about the company's approach to the field force, incentive schemes and call rates. The Panel did not consider that it had a specific allegation in this regard. AstraZeneca had referred to a previous case; Case AUTH/1714/5/05 wherein the Panel considered that the company's activity targets were set so high that campaign notes advocated a course of action likely to lead to a breach of the Code. A breach of the Code had been ruled. Pursuant to Case AUTH/1714/5/05 AstraZeneca submitted that it had withdrawn all frequency targets for the remainder of 2005 and all coverage and frequency based incentive schemes. The Panel noted that whilst the current OneView objective document for primary care Q3 indicated that coverage and frequency targets were set at zero, call volume targets were stated. The Panel noted that a recent call frequency briefing delivered pursuant to Case AUTH/1714/5/05 set out the relevant requirements of the Code. The link between sales and frequency was highlighted. The removal of frequency objectives was mentioned. Representatives were instructed to achieve 100% coverage of target list in 2005.

The Panel noted AstraZeneca's submission that the statement made by the senior executive was part of a personal anecdote during a motivational presentation in 2002 to encourage a more dynamic approach. Some of those who had been in the audience and now interviewed as part of the investigation into this complaint expressed concern that the statement could have been misinterpreted by inexperienced representatives whilst others described it as challenging and assertive. The Panel considered that the comments of the executive were inappropriate and likely to lead to a breach of the Code. High standards had not been maintained. Breaches of Clauses 15.9 and 9.1 were ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was used to indicate particular censure.

Complaint received **14 July 2005**

Case completed **22 October 2005**

CASE AUTH/1738/7/05

BRACCO UK v GE HEALTHCARE

Promotion of Visipaque and Omniscan

Bracco UK complained about two leavepieces issued by GE Healthcare, one for Visipaque (iodixanol) an X-ray contrast medium, and the other for Omniscan (gadodiamide), a contrast medium for magnetic resonance imaging (MRI).

In the Visipaque leavepiece entitled 'How do you manage cardiorenal risk?', the claim 'The osmolality of a contrast medium is an important pre-disposing factor for CIN [contrast medium induced nephrotoxicity]' appeared as the first bullet point on page 3 below the heading 'Visipaque (iodixanol) is isomolar' and was referenced to Thomsen and Morcos (2003). A bar chart beneath the claim depicted the osmolality of different contrast media (high osmolar contrast medium (HOCM), low isomolar contrast medium (LOCM) and isomolar contrast medium (IOCM)) in relation to blood. Visipaque was described as an IOCM. Bracco alleged that the claim, a quotation regarding osmolality, was taken out of context since it referred to HOCM compared to LOCM or IOCM contrast agents. There was currently no consensus on whether LOCM was better than IOCM. As such, the claim was misleading.

The Panel noted that the claim, although referenced to Thomsen and Morcos, was not presented as a quotation. The Panel did not accept GE Healthcare's submission that the statement made no claim that Visipaque was less likely to cause CIN than LOCM. The Panel considered that the claim would be interpreted in light of the prominent bar chart beneath which showed that Visipaque, an IOCM, was the only contrast medium with osmolality equal to blood and thus implied that the eight LOCMs and, to a greater extent, the two HOCMs depicted were more likely to induce CIN.

The data provided by GE Healthcare supported the claim with regard to the difference between HOCM and IOCM; the data with regard to LOCM was still developing. The Panel considered that whether the osmolality of a contrast medium was an important factor for CIN had not been resolved in favour of one accepted viewpoint with regard to IOCM and LOCM. The Panel considered that the claim 'The osmolality of a contrast medium is an important pre-disposing factor for CIN' within the context of the page was misleading in this regard and ruled a breach of the Code.

Upon appeal by GE Healthcare the Appeal Board did not accept the company's submission that no claim was made that Visipaque was less likely to cause CIN than LOCM. Like the Panel, the Appeal Board also considered that the claim at issue could not be considered in isolation and would be interpreted in the light of the prominent bar chart below it. In the Appeal Board's view the implied difference in propensity to cause CIN was emphasised by the use of different colours for each group of agents.

The Appeal Board examined all the data provided by GE Healthcare and drew the same conclusions as the Panel. The Appeal Board considered that the juxtaposition of the claim 'The osmolality of a contrast medium is an important pre-disposing factor for CIN' and the bar chart was misleading and upheld the Panel's ruling of a breach of the Code.

With regard to the bar chart discussed above, Bracco alleged that it was very unfair to compare Visipaque (270 and 320mgI/ml concentration) to agents at a much higher concentration because the higher the concentration, the higher the osmolality. The osmolality of iomeprol (Bracco's product lomeron) at 250mgI/ml was 435mOsm/kg and at 300mg/ml was 520mOsm/kg. The graph showed only the osmolality at iomeprol 350mg/ml (620mOsm/kg), and as such was misleading.

The Panel noted that the bar chart included only data for iodine 350mg/ml Iomeron as this was the most commonly used dose. The Panel did not know whether this was also the selection criteria for all other contrast media listed. The Panel noted that the basis upon which the contrast media had been selected was not clear from the bar chart and thus the comparisons were unfair in this regard. The Panel ruled that this was misleading in breach of the Code.

Upon appeal by GE Healthcare the Appeal Board considered that its ruling with respect to the claim 'The osmolality of a contrast medium is an important pre-disposing factor for CIN' was relevant. The Appeal Board noted the reason that the bar chart included only data for iodine 350mg/ml Iomeron but did not know whether all other contrast media listed had been chosen for the same reason ie the most commonly use dose. The basis upon which the contrast media had been selected was not clear and in association with the claim at issue above the Appeal Board considered that the comparisons were unfair, misleading and upheld the Panel's ruling of breaches of the Code.

Bracco noted that the claim 'Visipaque has less potential for major adverse clinical or cardiac events than the LOCM ioxaglate or iopamidol' appeared beneath the heading 'Contrast the cardiac risk' and above the subheading 'The COURT trial', (Davidson *et al* (2001). Data from the COURT trial followed. Bracco considered that iopamidol was mentioned with ioxaglate in a deliberate attempt to link the results of the COURT trial with iopamidol, which was not included in the trial. This implication was misleading.

The Panel noted that the claim at issue was referenced to Davidson *et al* (The COURT study) and Harrison *et al*. Data from the COURT study was presented. There was no subsequent mention of iopamidol or Harrison *et al*. The Panel considered that the claim misleadingly implied that the COURT study examined, *inter alia*, the effects of iopamidol and that was not so. A breach of the Code was ruled.

Upon appeal by GE Healthcare the Appeal Board noted that the claim at issue compared the adverse

clinical effects of two different medicines and cited data from two different studies, Davidson *et al* (the COURT study) and Harrison *et al*. The Appeal Board did not consider that it was unreasonable to cite the references at the end of the claim.

The Appeal Board noted that below the claim data from the COURT study was then presented under the prominent heading 'The COURT trial'. There was no subsequent mention of iopamidol or Harrison *et al*. The Appeal Board did not consider that the claim implied that the COURT study examined the effects of iopamidol. The Appeal Board did not consider that the claim at issue was misleading and ruled no breach of the Code.

Bracco noted that in the Omniscan leavepiece the claim 'Non ionic contrast media generally have low osmolality and are associated with a low rate of adverse reactions' was referenced to Chang *et al* (1992). Bracco alleged that the reference cited did not support the claim, Chang *et al* focussed on the correct terminology to define products dissociating in solution from those which did not dissociate. The conclusions were that the terms non-ionic and ionic were appropriate and were indeed the best descriptors of these types of MR imaging contrast enhancing media. This was in breach of the Code.

The Panel noted that Bracco had alleged a breach of the Code on the basis that when promotional material referred to published data clear references needed to be given. The claim did not refer to a published study and thus a reference was not required. Thus there could be no breach of the Code.

Bracco noted that a bar chart of adverse events in the Omniscan leavepiece compared the retrospectively estimated incidence of adverse events for Omniscan (0.031%), Magnevist (0.067%) and Prohance (0.408%). The differences were not statistically significant. The bar chart was labelled N/S with the explanation 'N/S = not significant' appearing beneath the chart. Bracco alleged that the bar chart was a deliberate attempt to distort the data. The unusual scale, with a range 0-0.42, made the differences between products seem huge although they were non-significant. Bracco questioned whether this one study represented the general body of evidence, given that the sample sizes for Omniscan were ten times those of the other products. In addition, the adverse events rates were estimated and not measured. For all these reasons, this part of the brochure was in breach of the Code.

The Panel considered that use of a scale going from 0-0.42 gave the visual impression of a marked difference between the products. This was not so. The differences were not statistically significant. The reference N/S at the top of the bar chart did not negate the misleading impression given. Thus the Panel ruled a breach of the Code which was upheld on appeal by GE Healthcare.

Bracco noted that a bar chart in the Omniscan leavepiece presented data relating to tissue histopathology after injecting mice; the data was from animal studies injecting contrast sub-cutaneously. This was outside the product licence and thus the relevance had to be questioned. Bracco alleged a breach of the Code.

The Panel considered that the presentation of the animal data was misleading. It was not sufficiently clear that the data were from mice, reference to which appeared in small print adjacent to the bar chart. The relevance to the clinical situation was questionable. A breach of the Code was ruled.

Upon appeal by GE Healthcare the Appeal Board noted that extravasation data would be of interest to health professionals. Although the Appeal Board accepted that it would not be ethical to conduct a clinical trial on the effects of extravasation, the relevance of the animal data to patients was not clear. GE Healthcare did not provide any observational data from accidental extravasation of contrast media to show that the data in mice echoed what might be observed in patients. The Appeal Board considered that it was not sufficiently clear that the data at issue came from mice. The Appeal Board considered that the claim 'Non-ionic Omniscan can cause less tissue damage than ionic Magnevist' implied that a difference between the two agents in favour of Omniscan had been proven. This was not so. Overall the Appeal Board considered that the presentation of the data was misleading as alleged. The Appeal Board upheld the Panel's ruling of a breach of the Code.

Bracco alleged that the claim of a 'wide range of packaging formats' for Omniscan was exaggerated given that only two formats were displayed.

The Panel considered that it was misleading and exaggerated to illustrate a claim for a wide range of packaging formats for flexibility and ease of use with a picture of only two, a glass vial and a soft pack. A breach of the Code was ruled.

Bracco UK Ltd complained about two leavepieces issued by GE Healthcare, one for Visipaque (iodixanol) (ref JB1193/MB001071/05 UK) and the other for Omniscan (gadodiamide) (ref JB1192/MB001221/0S UK)).

Visipaque was an X-ray contrast medium and Omniscan was a contrast medium for magnetic resonance imaging (MRI).

A Leavepiece for Visipaque entitled 'How do you manage cardiorenal risk?'

1 Claim 'The osmolality of a contrast medium is an important pre-disposing factor for CIN [contrast medium induced nephrotoxicity]'

This claim appeared as the first bullet point on page 3 below the heading 'Visipaque (iodixanol) is isomolar' and was referenced to Thomsen and Morcos (2003). A bar chart beneath the claim depicted the osmolality of different contrast media (high osmolar contrast medium (HOCM), low isomolar contrast medium (LOCM) and isomolar contrast medium (IOCM)) in relation to blood. Visipaque was described as an IOCM.

COMPLAINT

Bracco alleged that the claim at issue, a quotation regarding osmolality was taken out of context since it referred to HOCM compared to LOCM or IOCM contrast agents. There was currently no consensus on whether LOCM was better than IOCM. As such, the claim was misleading and in breach of Clause 7.3 of the Code.

RESPONSE

GE Healthcare noted that the leavepiece 'How do you manage cardiorenal risk?' had been used from January 2005 by account managers for face-to-face detailing and as a leavepiece with interventional cardiologists (doctors). It had also been used on exhibition stands at meetings in the UK attended by interventional cardiologists.

GE Healthcare noted that the claim at issue was not a direct quote from Thomsen *et al* and was not presented as such. It was a claim supported by the cited reference.

GE Healthcare noted that Bracco appeared not to object to the implication that HOCM was more likely to cause CIN than LOCM; there were numerous papers supporting this fact. The statement made no claim that the IOCM, Visipaque, was less likely to cause CIN than LOCM.

Thomsen and Morcos was an overview of reports from the Contrast Media Safety Committee of the European Society of Urogenital Radiology (ESUR), which had looked at the effects of contrast media on the kidney, including the prevention of CIN.

GE Healthcare noted that whilst the pathophysiology of CIN was complex and not completely understood, it was generally accepted to be due to a combination of a direct toxic effect on the renal tubular epithelium and a reduction in renal perfusion. In discussing the mechanisms responsible for a reduction in renal perfusion, Thomsen and Morcos described the marked natriuresis and diuresis caused by HOCM, which activated the tubuloglomerular feedback (TGF) response. This led to vasoconstriction of the glomerular afferent arterioles causing a decrease in the glomerular filtration rate and an increase in renal vascular resistance. The authors stated that the activation of TGF was dependent on the osmolality of the contrast medium, and LOCM, which was hyperosmolar to blood, might also elicit this response. The authors also stated that IOCM, which was isosmolar to blood, did not.

GE Healthcare noted that Bracco had stated that there was currently no consensus on whether LOCM was better than IOCM. GE Healthcare assumed that Bracco was questioning whether there was a consensus on whether IOCM was better than LOCM with regard to CIN. The statement made no claim that the IOCM, Visipaque, was less likely to cause CIN than LOCM.

Thomsen and Morcos discussed a number of recommendations to prevent CIN including the use of IOCM instead of LOCM or HOCM. GE Healthcare submitted that by taking a conservative approach it had chosen not to use this recommendation in its promotional materials. There was however strong, growing evidence to support the use of IOCM in patients at high risk of CIN including the prospective randomised controlled NEPHRIC study (Aspelin *et al* 2003) which was cited in the leavepiece.

GE Healthcare submitted that other evidence supporting the benefits of IOCM compared to LOCM with regards to renal function included Chalmers and Jackson (1999), Sang-Ho *et al* (2005) and a meta-analysis by Clauß *et al* (1995) which reviewed data from 14 randomised, double-blind studies to compare a number of LOCM with an IOCM, iotrolan, that was no longer available for angiography use. The authors concluded that the iso-osmolar agent had less effect on renal function than the low osmolar comparators. It should be noted that no prospective randomised trials had yet shown any advantage for a LOCM compared to an IOCM with regard to benefits in renal safety.

GE Healthcare submitted that there was an increasing number of experts in the UK producing guidelines advising that patients at high risk of CIN were given IOCM rather than LOCM, and examples of independently produced local guidelines, giving similar advice were provided.

In summary, GE Healthcare submitted that Thomsen and Morcos advised that osmolality was an important factor for CIN. No comparative claim was made for IOCM against LOCM, but there was growing evidence that IOCM might have an advantage in certain groups of patients. Consequently, the claim in question was an accurate reflection of the paper and was not in breach of Clause 7.3 of the Code.

PANEL RULING

The Panel noted that the claim in the leavepiece provided by GE Healthcare was different to that at issue and read 'The osmolality of a contrast medium is an important factor for CIN'. The page was otherwise identical, save for the omission of the non-proprietary name in the heading.

The Panel noted that the claim was not presented as a quotation in the leavepiece. It was referenced to Thomsen and Morcos. The Panel did not accept GE Healthcare's submission that the statement made no claim that Visipaque was less likely to cause CIN than LOCM. The Panel considered that the claim would be interpreted in light of the prominent bar chart beneath which showed that Visipaque, an IOCM, was the only contrast medium with osmolality equal to blood and thus implied that the eight LOCMs and, to a greater extent, the two HOCMs depicted were more likely to induce CIN.

The Panel examined all the data provided by GE Healthcare. There was some data to support the claim at issue with regard to the difference between HOCM and IOCM. The data with regard to LOCM was still developing. The Panel considered that whether the osmolality of a contrast medium was an important factor for CIN had not been resolved in favour of one accepted viewpoint with regard to IOCM and LOCM. The Panel considered that the claim 'The osmolality of

a contrast medium is an important pre-disposing factor for CIN' within the context of the page was misleading in this regard and ruled a breach of Clause 7.3.

APPEAL BY GE HEALTHCARE

GE Healthcare submitted that this item had been used from January 2005 by account managers for face-to-face detailing and as a leavepiece, exclusively with specialist physicians who used contrast media in percutaneous coronary intervention. It had also been used on exhibition stands at meetings in the UK, exclusively those attended by such specialists. This leavepiece had not been used with other customers; GE Healthcare noted that it had been designed to be appropriate for those specialist physicians who used contrast media for this type of procedure. GE Healthcare noted that the supplementary information to Clause 12.1 of the Code stated that promotional material should be tailored to the audience to whom it was directed.

GE Healthcare noted that Visipaque was an X-ray contrast medium authorized for intra-arterial, intravenous and intrathecal use in adults (cardioangiography, cerebral angiography, peripheral arteriography, abdominal angiography, urography, venography, CT-enhancement and myelography). Visipaque was also authorized for intra-arterial and intravenous use in children (cardiography, urography and CT-enhancement). Iodixanol, was a non-ionic, water soluble dimer which in all available concentrations had a lower osmolality than whole blood. Ready-to-use solutions of Visipaque were made isotonic by the addition of electrolytes (sodium and calcium).

GE Healthcare submitted that administration of X-ray contrast media represented a risk for the development of nephrotoxicity (CIN). The mechanisms for the pathogenesis of CIN were complex, but osmotic, haemodynamic and tubular effects were the three main contributing factors. Contrast media also stimulated endogenous substances like endothelin, adenosine, calcium ions and oxygen free radicals which had been proposed as mediators for the reduction in glomerular filtration rate (GFR). The diagnosis of CIN was usually based on the change in serum creatinine level from the patient's own baseline level before the procedure, and the threshold used most commonly in the literature was an increase in serum creatinine of ≥ 44.2µmol/l.

GE Healthcare submitted that the osmolality of contrast media was considered an important factor in the pathogenesis of CIN. In spite of an improvement in the chemical structure of contrast media, from HOCM (1500mOsm/kg) to LOCM (about 700mOsm/kg), the incidence of CIN was still high in at-risk patients ie those with renal impairment, diabetes and especially the combination of these two conditions. In these patients, CIN was reported to be in the range of 12-40% after administration of LOCM.

GE Healthcare submitted that CIN remained the third leading cause of hospital-acquired acute renal failure, contributing to an increased mortality risk. In order to reduce the osmotic effects and nephrotoxicity of contrast media, the non-ionic dimeric contrast media iodixanol (Visipaque) was developed. The osmotic diuretic effect was reduced with iodixanol as compared to LOCM. The haemodynamic side effects of IOCM were even lower than with LOCM and injection related pain and heat sensations also occurred less frequently. With an ageing population and with the high incidence of diabetes and its related complications, particularly on the kidneys, there was a need for a contrast medium with a lower incidence of CIN than that known to occur with LOCM.

GE Healthcare noted the claim 'The osmolality of a contrast medium is an important factor for CIN' and that the Panel concluded in its ruling that this claim was misleading, and that the bar chart beneath the statement 'The osmolality of a contrast medium is an important factor for CIN' implied that the eight LOCM and the two HOCM depicted were more likely to induce CIN than the IOCM Visipaque. GE Healthcare did not consider that medical professionals with relevant background and experience would make such an inference based upon these facts, and so the advertisement did not make a comparative claim as suggested by the Panel; it was factual and should not be deemed misleading.

GE Healthcare stated that the purpose of the bar chart was to highlight physical properties of each contrast medium with respect to osmolality. Both the statement and the chart were accurate and important information for the clinicians practicing in this area. Nevertheless, even if the Panel's interpretation that a comparative claim had been made was upheld, the evidence provided below supported the benefits of IOCM over HOCM and LOCM in patients who were at risk of CIN.

GE Healthcare stated that those with an interest in contrast induced nephropathy (CIN) generally accepted that osmolality was an important factor in its causality; though of course not the only factor. Indeed, there were an increasing number of experts in the UK who saw the role of osmolality in the development of CIN as so important that they had independently produced evidence-based guidelines which advised that patients at high risk of CIN were given IOCM rather than LOCM. GE Healthcare provided copies of three such protocols from different regions of the UK.

GE Healthcare submitted that this was not just an issue in the UK; opinion leaders around the world had studied and written extensively in this area. Liistro *et al* (2003) stated that 'The process of minimizing the adverse effects associated with CM [contrast medium] administration has focused on lowering their osmolality and altering the ionic nature of these agents whilst maintaining an iodine concentration compatible with radiological examinations …' ' … The physicochemical properties of CM, in particular the higher osmolality of some compounds compared with plasma and their ionic charge, can results in multisystemic effects: osmotic shifts and changes in the ion balance, damage to the vascular endothelial cells which may results [sic] in a shift from an anticoagulant to a procoagulant state, hemodynamic and electrophysiological effects and, above all, effects on the renal function. Modern CM

are formulated to minimize these effects. In particular, the iso-osmolality of third-generation CM provides a profile that is closer to physiological than conventional CM'. The authors went on to state 'The risk of developing CIN varies according to the physicochemical properties of the CM used. As the renal damage associated with CM largely results from the diuretic and hypertonic effects on the kidney, which are in turn related to the agent's osmolality, it is not surprising that the risk of renal impairment is greatest with the use of high-osmolar CM (HOCM), moderate with low-osmolar CM (LOCM) and low with iso-osmolar CM.'

GE Healthcare noted that Goldfarb (2005) discussed the risk factors, pathophysiology and prevention of CIN. Goldfarb stated 'The osmolality of contrast media – and, therefore, the osmolar load delivered to the renal tubules – appears to be critical in the development of CIN. Our study showed that the use of low-osmolar contrast material (LOCM) reduced the incidence of CIN by almost two thirds. Other studies, including a meta-analysis of 25 individual trials, have also concluded that use of LOCM reduces the risk of developing CIN. Isosmolar contrast material appears to further reduce the risk of CIN'. To prevent CIN, Goldfarb suggested using the lowest possible dose of contrast medium, and selecting, 'low-osmolar – or, ideally, isosmolar – contrast material'.

GE Healthcare submitted that to further emphasise how the importance of osmolality in CIN was generally accepted, it enclosed statements which had been prepared by experts in the fields of interventional cardiology, interventional radiology and nephrology, all of whom had a special interest in contrast-induced nephropathy. The evidence supporting the benefits of IOCM with regard to CIN had also resulted in changes to the UK SPC for Visipaque; this was discussed in more detail below.

GE Healthcare submitted that the pathophysiology of CIN was generally accepted to be due to a combination of a direct toxic effect on the renal tubular epithelium and a reduction in renal perfusion. In discussing the mechanisms responsible for a reduction in renal perfusion, Thomsen and Morcos described the marked natriuresis and diuresis caused by high osmolar agents, which activated the tubuloglomerular feedback (TGF) response. This led to vasoconstriction of the glomerular afferent arterioles causing a decrease in the glomerular filtration rate and an increase in renal vascular resistance. The authors stated that the activation of TGF was dependent on the osmolality of the contrast medium, and LOCM, which were hyperosmolar to blood, might also elicit this response. The authors also stated that 'In contrast, iso-osmolar dimers, which induce only a mild natriuresis and diuresis, do not activate this mechanism'. GE Healthcare noted that Thomsen and Morcos, used to support the statement 'The osmolality of a contrast medium is an important factor for CIN', was an overview of reports from the Contrast Media Safety Committee of the European Society of Urogenital Radiology (ESUR), who had looked at issues around the effects of contrast media on the kidney, including the prevention of CIN.

GE Healthcare submitted that there was a significant body of clinical evidence that IOCM were less likely to cause CIN than LOCM in high risk patients. Aspelin *et al* and Chalmers and Jackson demonstrated that Visipaque had advantages over the LOCM iohexol in terms of renal function in high risk patients (those with diabetic nephropathy). Chalmers and Jackson demonstrated that of 124 patients undergoing renal or peripheral angiography, 15% of those who received Visipaque experienced a rise in serum creatinine of more than 10% in the week following angiography, compared with 31% in the iohexol group ($p<0.05$). However, only about a third of these patients were at high risk. Aspelin *et al*, the NEPHRIC study, examined 129 high risk patients (those with diabetes and associated renal impairment) undergoing coronary (n=126) or aorto-femoral angiography (n=3), and in this study the mean peak increase in creatinine from baseline to day 3 post-procedure was 11.2µmol/l in the Visipaque group and 48.2µmol/l in the iohexol group (p=0.001). The authors stated that iodixanol was significantly less nephrotoxic than iohexol. The mean change in the serum creatinine concentration between day 0 and day 7 (when it was measured in 116 patients) was 6.3µmol/l in the Visipaque group and 21.4µmol/l in the iohexol group (p=0.003). When the most commonly used definition of contrast-induced nephropathy was used, (an increase in the serum creatinine concentration of at least 44µmol/l), the incidence of nephropathy was 3% in the Visipaque group (2/64) and 26% in the iohexol group (17/65) (p=0.002). The odds ratio for nephropathy in the Visipaque group as compared with the iohexol group was 0.09 (95% confidence interval, 0.02 to 0.41). Ten patients in the iohexol group (15%) but none in the iodixanol group had an increase in serum creatinine concentration of at least 88.4µmol/l.

GE Healthcare submitted that further evidence supporting the benefits of IOCM compared to LOCM with regards to renal function included Sang-Ho *et al*, an abstract which compared the IOCM Visipaque with the LOCM ioxaglate in 282 patients undergoing coronary angiography, and showed a reduction in the incidence of CIN with Visipaque of 60% relative to the LOCM ioxaglate. In a subgroup of 109 patients with diabetes, Visipaque reduced the incidence of CIN by over 70% compared to the LOCM ioxaglate.

A meta-analysis by Clauß *et al* reviewed data from 14 randomised, double-blind studies to compare a number of LOCM with an IOCM, iotrolan that was no longer available for angiography use. The authors concluded that the IOCM had less effect on renal function than the LOCM comparators.

GE Healthcare submitted that Sinha *et al* (2004) the Prevention of Radiocontrast-Induced Nephropathy Trial (PRINT) was a prospective, double-blind, randomised, controlled trial in 70 patients with pre-existing renal insufficiency undergoing coronary angiography with or without intervention (PCI), and compared the IOCM Visipaque and the LOCM iohexol. The trial showed a relative risk reduction for Visipaque versus the LOCM for acute renal failure (CIN) of 77.8% at 2 days and a cumulative reduction of 61.5% at 7 days ($p<0.04$).

GE Healthcare submitted that Lim *et al* (2004) was a retrospective analysis of 7769 unselected patients who underwent PCI in one Canadian centre over the previous 4 years. When data from the first 3 years, where the LOCM iohexol was used exclusively, were compared with the data from the final year, when the IOCM Visipaque was used exclusively, the incidence of CIN was seen to have dropped by 30.5% in the final year.

GE Healthcare submitted that a meta-analysis by Stacul *et al* (2004) assessed in a large population whether the IOCM Visipaque was less nephrotoxic than LOCM and identified predictors for CIN. Data from 2727 adults undergoing angiography in 16 prospective, double blind comparative trials were analysed. CIN, defined as an increase in serum creatinine of ≥44.2µmol/l occurred less frequently after Visipaque than LOCM (1.4% vs. 15.5%, p=0.0004), including in patients with pre-existing renal impairment (2.8% vs. 8.4%, p=0.001) and patients with diabetic nephropathy (3.5% vs 15.5%, p=0.003). The authors concluded that the meta-analysis showed lower incidences of CIN following angiography with the IOCM Visipaque versus LOCM.

GE Healthcare was aware that Bracco claimed that not all LOCM had the same properties with regard to renal safety and the risk of CIN, and therefore questioned the validity of the NEPHRIC study. Bracco claimed that NEPHRIC demonstrated less the benefits of Visipaque over LOCM, than that iohexol had a particularly high risk of CIN compared to other LOCM. Bracco had in the past made this argument based on data on file and abstract data from an analysis of pooled study data, which was not well conducted or thorough. This pooled analysis of 11 studies involving 992 patients was presented in abstract in 2004. The selection of studies for the analysis was fundamentally flawed. In order to be able to combine results from different studies to produce a valid overall quantitative analysis of the renal affects of contrast media, the studies themselves must be sufficiently similar to one another. This was not the case; the 11 studies had very different study populations, with differing baseline serum creatinine ranges and different proportions of patients with concomitant illnesses such as diabetes mellitus and renal impairment. These factors significantly affected the incidence of CIN. The study methodology differed, the statistical methods varied, follow-up times and clinical endpoints also varied significantly and all these factors would have a significant effect on the results of a study. In some cases only the placebo arms of studies were used, as the studies were designed not to look at the renal effects of different contrast media but at the reno-protective effects of other agents. Importantly, the definition of CIN that was used also varied between studies. These were clearly 'cherry-picked' data, use of which did not give a fair, balanced and objective impression and was highly misleading. It was also apparent that the literature search was not exhaustive. The authors had not included unpublished studies, which introduced publication bias, and a contrast medium was excluded if less than three studies involving its use were identified, no matter how many patients this involved. No rationale for this strategy was made in the abstract or on the stand panel.

GE Healthcare submitted that there were no randomised controlled trials that showed the opposite finding to the benefits of IOCM seen in NEPHRIC and the other evidence outlined here, or even showed an equivalent of risk of CIN between any of the many available LOCM and the IOCM Visipaque in high risk patients. There was also no sound evidence that iohexol had a higher risk of CIN than any of the other LOCM. Iohexol had been available for more than 20 years, and was an obvious choice as a comparator LOCM when studies of the safety aspects of contrast media were performed, partly because of its excellent safety record, and also as it was the most widely-studied LOCM available. Iohexol was the first LOCM to demonstrate, in a large multicentre study, a difference in renal toxicity between LOCM and HOCM (Rudnick *et al* 1995). Interestingly, another large multicentre study, Schwab *et al* (1989), failed to show a difference in renal toxicity between the HOCM diatrizoate and the LOCM iopamidol. All the evidence suggested that the risk of CIN was very similar with all the available LOCM, including iohexol, and that this was essentially a class effect of LOCM.

GE Healthcare noted that the summaries of product characteristics (SPCs) of all LOCM were essentially the same with regard to renal safety. However, following the results of NEPHRIC, a revision to the Visipaque UK SPC was approved to include the text 'Visipaque induces only minor effects on renal function in patients. In 64 diabetic patients with serum creatinine levels of 115-308µmol/L, Visipaque use resulted in 3% of patients experiencing a rise in creatinine of ≥44.2µmol/L and 0% of the patients with a rise of ≥88.4µmol/L. The release of enzymes (alkaline phosphatase and N-acetyl-ß-glucosaminidase) from the proximal tubular cells is less than after injections of non-ionic monomeric contrast media [LOCM] and the same trend is seen compared to ionic dimeric contrast media [HOCM]. Visipaque is also well tolerated by the kidney'.

GE Healthcare submitted that the evidence supporting the benefits of IOCM with regard to CIN had also resulted in similar SPC changes in other countries, including France and Spain.

In summary GE Healthcare stated that Thomsen and Morcos, a review from the influential and respected ESUR, advised that osmolality was an important factor for CIN. Although a claim for IOCM over LOCM was not the intention of this page, given the evidence supporting the benefits of IOCM over HOCM and LOCM in high risk patients and the expert advice available from respected bodies on this subject, this page was an accurate reflection of the available evidence on the subject, was not misleading and was not in breach of Clause 7.3 of the Code.

COMMENTS FROM BRACCO

Bracco noted its complaint and stated that its position remained unchanged. It firmly believed that the Visipaque leavepiece which was the subject of this appeal was in breach of the Code as outlined above. Indeed its position was further strengthened by the Panel's rulings.

Bracco noted that a piece of promotional material must be able to stand alone and alleged that in its appeal, GE Healthcare had offered significant additional references that were irrelevant because they were not cited in the leavepiece at issue. However despite its concerns about the volume of documentation, Bracco gave further reasons to rebut GE Healthcare's appeal below.

Bracco noted that the osmolality of LOCM depended on the iodine strength of the solution and ranged from 290mOsm/kg (ie isotonic to human blood) to 915mOsm/kg (ie 3 times that of human blood). Patients at higher than usual risk for the development of CIN might be exposed to LOCM solutions of any iodine strength. In its appeal GE Healthcare claimed that 'this piece has been specifically designed for, and had been used exclusively with those clinicians who use contrast media in percutaneous coronary angiography with or without intervention (PCI) …This chart represented the relative osmolalities of different contrast media, at iodine concentrations most commonly used in this area of practice, 320-370mgI/ml'.

Bracco alleged that the statement was not correct, since the leavepiece did not state that it was specifically tailored or directed only to clinicians who used contrast media in percutaneous coronary angiography with or without intervention. There was no proof that the leavepiece did not get into the hands of other clinicians, who might use contrast solutions at higher (eg 400mgI/ml) or lower (300mg/ml or below) iodine concentration (eg angiographers or interventional radiologists).

- Cardiologists who used radiographic contrast media in percutaneous coronary angiographies also used contrast media in other procedures, such as renal or peripheral angiographies, and they indeed used solutions at higher (eg 400mg/ml) or lower (≤ 300mg/ml) iodine concentration either for coronary angiography or for renal or peripheral angiography.

Bracco noted in the two studies that GE Healthcare used to support its claim that Visipaque was less nephrotoxic than LOCM, ie Aspelin *et al*, the NEPHRIC study, and Chalmers and Jackson:

- Iodine concentrations lower than 320mg/ml had been used (Visipaque 270 and Omnipaque 300 in Chalmers and Jackson);

- Patients did not only undergo cardiac angiography procedures, but also procedures like aorto-femoral angiography (in both studies) or renal angiography (Chalmers and Jackson). Incidentally, Aspelin, first author and principal investigator of the NEPHRIC study, and Chalmers and Jackson were all radiologists who performed angiography procedures as well as CT exams, excretory urographies and other radiographic examinations.

Bracco alleged, therefore, that the iodine concentrations in the bar chart had been selected to show a big difference in osmolality between Visipaque and the other CM, to reinforce the message that osmolality was an important pre-disposing factor for CIN and to imply that the lower the osmolality, the lower was the contrast media nephrotoxicity.

Bracco noted that GE Healthcare then stated that even if a comparison had been made, such a claim would be supported by the evidence provided in the appeal '… the evidence [GE Healthcare] provided below supported the benefits of IOCM over HOCM and LOCM in patients who were at risk of CIN'. To support its position, GE Healthcare also stated that 'It was generally accepted that amongst those with an interest in contrast-induced nephropathy (CIN) that osmolality was an important factor in its causality …'. Bracco alleged that this statement was incorrect as there was intense scientific debate about the role of osmolality in the development of CIN, in view of the existing evidence from both non-clinical and clinical studies that did not show a difference in nephrotoxicity between IOCM and LOCM, evidence that had not been given by GE Healthcare.

Bracco stated that all water-soluble, nephrotropic, iodinated contrast agents caused nephrotoxicity through direct toxic effect on the renal epithelial cells and contrast-induced renal medullary ischemia (Barrett 1994, Rudnick and Goldfarb 2003).

Bracco noted that contrast agents were shown to induce direct cytotoxic effects in the form of cytoplasmic vacuolization and lysosomal alteration in the proximal convoluted tubular cells and in the inner cortex (Rees *et al* 1997, Tervahartiala *et al* 1993, Tervahartiala *et al* 1997). Enhanced production of oxygen free radicals and a reduction in the activity of the antioxidant enzymes catalase and superoxide dismutase in the renal cortex of volume-depleted rats had been documented (Yoshioka *et al* 1992). Subsequently, oxidant-mediated injury had been suggested as a mechanism of cytotoxic effect in the pathogenesis of CIN. Lipid peroxidation of biologic membranes was also implicated in tissue injury. Significant morphologic alterations in proximal tubules, along with elevated renal levels of malondialdehyde, a marker of lipid peroxidation, were found in rats after exposure to contrast media (Parvez *et al* 1989).

Bracco stated that in an *in vitro* model using a renal epithelial cell line, DNA fragmentation (a marker of apoptosis) increased in cells exposed to HOCM, osmolality ≥ 1500mOsm/kg, and the degree of fragmentation was proportional to the osmolality of the contrast (Hizoh *et al* 1998). Solutions of mannitol and sodium chloride with osmolalities similar to the HOCM also caused DNA fragmentation, but to a lesser degree. This study indicated a direct cytotoxic effect of contrast media independent of hypoxia, which to a large extent might be related to the hyperosmolality of HOCM. In contrast, experiments in other *in vitro* models demonstrated that LOCM (osmolality < 915mOsm/kg), but not equiosmolar mannitol (ie mannitol solutions still hyperosmolal to human blood), resulted in mitochondrial dysfunction of renal tubular cells, suggesting that the nephrotoxic effect of LOCM was related to some property other than osmolality (Hardiek *et al* 2001). Subsequent experiments comparing the renal effects of IOCM with LOCM or even HOCM could not demonstrate a reduction in renal abnormalities with the isotonic

nonionic dimers, confirming that factors other than osmolality played a role in CIN. In many of these studies, the IOCM produced more nephrotoxic abnormalities than those seen with LOCM and HOCM, possibly because of their increased viscosity (Barrett).

Heinrich *et al* (2005) compared the cytotoxic effects of dimeric and monomeric iodinated contrast media on renal tubular cells *in vitro* with regard to osmolality. Proximal tubular epithelial cell from kidneys were incubated with ioxithalamate (HOCM, osmolality: 1860mOsm/kg), ioversol-300 (LOCM, iodine 300mg/ml, osmolality: 651mOsm/kg), iomeprol-300 (LOCM, iodine 300mg/ml, 520mOsm/kg), iomeprol-150 (LOCM, iodine 150mg/ml, osmolality: 301mOsm/kg, isotonic to blood), iodixanol (IOCM, osmolality: 290mOsm/kg, isotonic to blood), iotrolan (IOCM, osmolality: 300mOsm/kg, isotonic to blood), and hyperosmolar mannitol solutions (one at 1860mOsm/kg and one at 520mOsm/kg) for 1-24 hours at concentrations from iodine 18.75 to 150mg/ml. Cytotoxic effects were assessed using a standard methodology to assess cell damage, ie, the 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay. The conversion of MTT, a tetrazolium salt, into formazan depended on the activity of a group of mitochondrial dehydrogenases and, thus, was an indicator of cell metabolic activity. The lower the conversion of MTT, the higher was the cytotoxicity of the contrast media. Data were analyzed with one-way analysis of variance. The study showed that, at equal iodine concentrations, ioxithalamate showed stronger cytotoxic effects than other contrast media (MTT conversion for ioxithalamate was 4% vs that for ioversol-300 of 32%, that for iomeprol-300 of 34%, that for iodixanol of 40%, and that for iotrolan of 41% of undamaged control cells at 75mg/ml, iodine n=61-90, $p < 0.001$). There was no significant difference between the LOCM and IOCM tested ($p > 0.05$). At equal molarity, the isotonic dimeric contrast media induced significantly stronger cytotoxic effects than did low-osmolar monomeric contrast media (40% for iodixanol and 41% for iotrolan vs 64% for ioversol and 59% for iomeprol-300 at 98.5mmol/l, n=61-75, $p < 0.001$). At equimolar concentrations, both dimeric contrast media showed stronger cytotoxic effects than did iso-osmolar formulation of iomeprol-150 (51% for iodixanol and 50% for iotrolan vs 77% for iomeprol-150 at 98.5mmol/l, n=35-40, $p < 0.001$). Mannitol solutions induced weaker cytotoxic effects than did corresponding contrast media compounds (74% for mannitol-520 vs 34% for iomeprol-300 and 41% for mannitol-1860 vs 4% for ioxithalamate, $p < 0.001$). The authors concluded that, besides hyperosmolality, direct cytotoxic effects of contrast media molecules contributed to their cytotoxic effects. Results of this study indicated that IOCM like iodixanol (Visipaque) and iotrolan (Isovist) had a greater potential for cytotoxic effects on proximal renal tubular cells *in vitro* than did LOCM like ioversol (Optiray) and iomeprol (Iomeron).

As for the effects on renal haemodynamics, the deeper portion of the outer medulla was a region of the kidney particularly vulnerable to ischemic injury (Brezis *et al* 1984). Kidney perfusion was very high for the cortex, but the medullary portions were maintained at the verge of hypoxia, with pO_2 levels which could be as low as 20mmHg (Brezis and Rosen 1995). The relatively high oxygen requirements due to salt reabsorption and the extremely low oxygen tension offered an explanation to the reason for the vulnerability of the outer medullary portion of the nephron.

The mechanism by which contrast media might lead to medullary ischemia and medullary hypoxia was twofold: a) they might cause renal vasoconstriction (Heyman *et al* 1988, Heyman *et al* 1991 and Heyman 1994), and b) they have shown an ability to cause red blood cell aggregation, which could further impair oxygen delivery (Liss *et al* 1996). IOCM, the nonionic dimers, had been reported to cause more red blood cell aggregation, cessation of flow in the renal microcirculation, and reduction in renal blood flow compared to LOCM (Parvez *et al*, Deray *et al* 1999 and Laissy *et al* 2000). Other experimental studies confirmed that IOCM might worsen medullary hypoxemia more than LOCM and even HOCM (Lancelot *et al* 1999, Liss *et al* 1998). A diminished transit time of these highly viscous CM in the tubule might lead to a decrease in glomerular filtration rate and in renal blood flow by compression of peritubular vessels (Ueda *et al* (1993)). Also, the diminished tubular transit time of the nonionic dimers may result in an increased time for solute transport and increased oxygen utilization (Barrett).

Bracco noted that the LOCM iohexol was found to be more toxic than other LOCM on proximal tubule vacuolization (Tervahartiala *et al* 1997, Beaufils *et al* 1995) and capillary congestion. The relationship of these histologic changes to the functional changes in renal blood flow and glomerular filtration rate was unclear.

In conclusion, Bracco stated that the available non-clinical, experimental studies had shown that: all iodinated contrast media might cause nephrotoxic effects through direct cytotoxic effects and renal medullary ischemia; factors other than osmolality were more important in the pathogenesis of CIN when the osmolality of contrast solutions was < 1000mOsm/kg; IOCM, like iotrolan (Isovist) and iodixanol (Visipaque), might worsen medullary hypoxemia and produce more nephrotoxic abnormalities than LOCM.

Bracco noted that GE Healthcare had stated that 'There was significant body of evidence that IOCM were less likely to cause CIN than LOCM in high risk patients. Aspelin *et al* and Chalmers and Jackson demonstrated that Visipaque had advantages over the LOCM iohexol in terms of renal function in high risk patients (those with diabetic nephropathy)'. Bracco noted that GE Healthcare briefly reported the results of both studies but later admitted that in Chalmers and Jackson 'only about a third of these patients were at high risk'. Also, GE Healthcare had reported that Chalmers and Jackson was conducted in 124 patients but did not mention that one patient in the Visipaque group was excluded because he was given both Visipaque and Omnipaque, six patients were excluded because they had baseline serum creatinine values below 1.7mg/dL, and 15 patients were excluded

because no blood sample was obtained in the 7 days following the contrast-enhanced procedure, so that data analysis was finally conducted in 102 patients. GE Healthcare did not mention that iodixanol-270 (Visipaque 270, iodine 270mg/ml) or iodixanol-320 (Visipaque-320, iodine 320mg/ml) were compared to iohexol-300 (Omnipaque-300, iodine 300mg/ml), while in the NEPHRIC study Visipaque 320 was compared to Omnipaque 350. Also, GE Healthcare did not mention that in Chalmers and Jackson the doses of contrast were unusually low (53ml Omnipaque on average, 60ml Visipaque, 16 and 17g iodine in total). Last but not least, it was well known that in the vast majority of clinical trials (NEPHRIC included), CIN was defined as a relative rise in serum creatinine ≥25%, or as an absolute increase ≥0.5mg/dl from baseline (McCullough and Sandberg, 2003 and Thomsen 2003). However, GE Healthcare had not mentioned that the Visipaque and Omnipaque groups did not significantly differ for serum creatinine increases by 25% or higher (4% Visipaque, 10% Omnipaque), ie the two groups did not differ when one of the standard CIN endpoints was used.

Bracco stated that only the NEPHRIC study (Aspelin *et al*) showed that Visipaque was less nephrotoxic than Omnipaque in 129 patients with renal impairment (baseline serum creatinine: 1.5-1.6mg/dl) and diabetes mellitus. The incidence of CIN, defined as an absolute increase ≥0.5mg/dl from baseline, was significantly lower with Visipaque (3%) compared to Omnipaque (26%, p = 0.002). Six patients (9%, the highest rate ever reported) suffered clinical acute renal failure related to the use of Omnipaque and had to undergo hemodialysis. Three of those patients recovered, two died, one had persistent renal failure. There were no additional head-to-head comparisons showing that Visipaque was less nephrotoxic than other LOCM in this patient population.

On the contrary, Bracco noted that in Briguori *et al* (2005) 225 patients with chronic renal insufficiency (serum creatinine >1.5mg/dl or an estimated glomerular filtration rate <60ml/min), underwent coronary and/or peripheral procedures with either Xenetix (iobitridol, 915mOsm/kg; iobitridol group; n=115) or Visipaque (iodixanol group; n=110). Baseline serum creatinine levels were similar in the 2 groups (iobitridol group = 1.70mg/dl; iodixanol group = 1.73mg/dl). Increase of at least 0.5mg/dl of the serum creatinine concentration occurred in 4/115 patients (3.5%) in the iobitridol group and 3/110 patients (2.7%) in the iodixanol group (p=1.00; odds ratio (OR) 0.58; 95% confidence interval, CI: 0.17–3.56). No case of renal failure requiring temporary dialysis occurred. There were 104 diabetic patients in this renally-impaired population, 49 in the iobitridol group and 55 in the iodixanol group. The principal characteristics of these patients were similar in the 2 groups. In these patients, CIN occurred in 2/49 (4.1%) in iobitridol group and in 3/55 (5.5%) in the iodixanol group (p = 1). Therefore, Visipaque was not less nephrotoxic than Xenetix even in the subset of patients with diabetic nephropathy.

Bracco noted that Briguori *et al* also assessed the rate of major adverse events (death, acute myocardial infarction, stroke, new or repeated coronary or peripheral revascularization and dialysis) at 12 months, in order to establish the long-term impact of contrast nephropathy. At 1-year follow-up, major adverse events occurred in 26 of the 115 (22.5%) patients in the iobitridol group and in 33 of the 110 patients (30%) of the iodixanol group (p = 0.22). Rate of death (8.7% vs. 11.8%, p = 0.66), myocardial infarction (1.7% vs 1.8%, p = 1.00), any percutaneous or surgical coronary or peripheral revascularization (10.5% vs 14.5%, p = 0.42), and end-stage renal failure requiring dialysis (2.6% vs 3.6%, p = 0.71), were similar in the two groups. Although not statistically significant, occurrence of major adverse events was higher in the 7 patients who experienced CIN (43% vs 26%, p = 0.38). Of note, end-stage renal failure requiring dialysis at 12 months occurred in 2 of the 7 (28.5%) patients who experienced CIN versus 5 of the 218 (2.3%) who did not experienced CIN (p = 0.016; OR 17.1; 95% CI 2.65-110.4).

Bracco noted that other head-to-head comparisons had not shown any significant difference between LOCM and Visipaque in renally-impaired patients. A randomised, double-blind comparison was conducted in patients with SCr values between 1.5 and 3mg/dl undergoing excretory urography with the nonionic dimer iodixanol (Visipaque) and the LOCM iopromide (Ultravist) (Carraro *et al* 1998). Renal function was assessed before and 1, 6, 24 and 48 hours, and 7 days after urography. Parameters included serum creatinine, as well as urinary tubular enzymes, alpha-1-microglobulin and albumin. Baseline serum creatinine was 1.6mg/dl on average in both groups. One non-diabetic patient in the Visipaque group developed CIN (serum creatinine increasing from 2.5 to 5.4mg/dl in 24 hours, returning to baseline by the 48-hour evaluation), none in the Ultravist group. Overall, urinary tubular enzymes did not change significantly in either treatment group.

Kolehmainen and Soiva (2003) had compared the IOCM Visipaque to the LOCM Xenetix in 50 (25/25) patients undergoing cranial or body computed tomography procedures. Both groups received similar volumes of contrast (113.3ml of iobitridol, 112.7ml of iodixanol), and had similar severe impairment of renal function at baseline (mean baseline serum creatinine: 2.7mg/dl in the iobitridol group, 2.6mg/dl in the iodixanol group; mean baseline creatinine clearance: 28.7ml/min in the iobitridol group vs 27.5ml/min in the iodixanol group). No differences were observed between the two agents. The incidence of increases of serum creatinine ≥ 0.5mg/dl was 17% with both Visipaque and Xenetix, while a decrease of creatinine clearance ≥ 25% was observed in 12.5% of the patients with both agents.

Bracco noted that GE Healthcare also reported the results contained in a number of abstracts to support the theory that Visipaque was less nephrotoxic than LOCM. However information in abstracts was more limited than that contained in peer-reviewed articles and so that it was difficult to judge the scientific value of such studies. However, GE Healthcare did not mention other abstracts that contained opposite information, such as an abstract by Lagerqvist *et al* (2005), who conducted a survey among Swedish

hospitals performing percutaneous coronary interventions. The IOCM Visipaque was used in 24,085 patients, the ionic LOCM Hexabrix (ioxaglate) in 22,294 patients, and the LOCM Omnipaque in 6,147 subjects. The incidence of renal failure within 12 months of the procedure was greatest for patients receiving Visipaque (1.8%). Hexabrix or Omnipaque caused a significantly lower rate of acute renal failure (0.9% and 1%, respectively, $p<0.001$ vs Visipaque). When adjusted for gender, age, diabetes, previous percutaneous coronary interventions and previous renal insufficiency, the risk ratio for Visipaque-treated patients remained significantly higher than for the other two contrast media. Hospitals switching contrast media to Visipaque experienced a doubling in renal failure after cardiac interventions.

Bracco noted that Spargias *et al* (2005) reported the results of a study of 231 patients with baseline serum creatinine ≥ 1.2mg/dl who were randomised to ascorbic acid or placebo. The IOCM Visipaque was used in 144 patients, the remaining 87 received LOCM (nonionic: iomeprol, Iomeron, n=40; iobitridol, Xenetix, n=30; iopentol, Imagopaque, n=8; ionic: ioxaglate, Hexabrix, n=9). CIN was defined as absolute rise of serum creatinine ≥ 0.5mg/dl or a relative rise ≥ 25% from baseline within 2-5 days post-procedure. CIN incidence was 14.6% for the IOCM Visipaque vs 14.1% for LOCM (iomeprol 10%; iobitridol 10%; iopentol 50%; ioxaglate 22.2%). The real scientific value of these studies would become clearer if and when they were published in peer-reviewed journals.

Bracco alleged, therefore, that GE Healthcare's statement that 'There were no randomized controlled trials that show the opposite finding to the benefit of IOCM seen in the NEPHRIC and the other evidence outlined here …' was incorrect.

- first, there was only one peer-reviewed paper, that of the NEPHRIC study, which showed that Visipaque was less nephrotoxic than Omnipaque;
- second, and more important, there were several head-to-head comparisons that did not show differences between Visipaque and nonionic monomeric LOCM in risk patients, including Chalmers and Jackson.

Bracco stated that in addition to head-to-head comparisons, recently published quantitative syntheses of multiple cohorts of renally impaired patients and analyses of the pooled data could not show any significant difference between Visipaque and the LOCM iopamidol following intra-arterial administration in risk patients. Solomon (2005) published a systematic overview of prospective, randomized, controlled studies of CIN in renally-impaired patients receiving intra-arterial doses of Visipaque or LOCM, and conducted a pooled analysis of the data from those studies to determine whether the osmolality of CM was predictive of CIN incidence. To be included in the review studies had to be: 1) published in English in a peer-reviewed journal; 2) be either randomized, double-blind comparisons of iodinated contrast media, or prospective, randomized studies of the safety and efficacy of measures to prevent CIN (hemofiltration, n-acetylcysteine or other drugs); 3) clearly report the exact number of patients who had received a specific nonionic contrast agent (eg iodixanol, iohexol, iopamidol, etc); 4) clearly report the exact number of patients who had received or not received any preventive measure other than hydration; 5) include adequate hydration before and after the procedure; 6) include patients with mean baseline serum creatinine levels between 1.5-3.5mg/dl and/or mean baseline creatinine clearance between 20 and 60ml/min; 7) employ intra-arterial contrast media administration; 8) define CIN endpoint as an absolute increase ≥ 0.5mg/dl or a relative increase ≥ 25% in serum creatinine over baseline at 1-7 days after the CM administration. Seventeen primary studies met the selection criteria, for a total of 1365 patients. Overall, the incidence of CIN was 16.9%. A multivariate logistic regression model showed that the risk of CIN was similar with the IOCM Visipaque and the LOCM Niopam (796mOsm/kg). The risk of CIN was significantly lower with Visipaque and Niopam compared to Omnipaque. The incidence of CIN with Omnipaque was also significantly higher than with Niopam, despite their similar osmolalities. The results of this systematic review of the literature were in line with the results of Briguori *et al* and with non-clinical, experimental evidence, so that the author concluded that factors other than osmolality played a role in the pathogenesis of CIN when LOCM or IOCM were used.

Bracco stated that Sharma and Kini (2005) conducted an extensive literature search in the main medical databases (MEDLINE, BIOSYS, EMBASE), using 'iodinated contrast media', 'contrast nephropathy' and 'renal or kidney impairment' as the main key words. Only prospective studies published in peer reviewed journals from January 2002 until March 2004 were considered for the pooled analysis, in order to ensure that similar medical standards had been used in all the studies. To be included in the analysis, studies had to have similar patient populations, similar design, and similar endpoints. The following additional criteria had to be met: a) patients had to have serum creatinine between 1.5 and 3.5mg/dl, and/or creatinine clearance between 20-60 ml/min; b) contrast media had to be administered intra-arterially for diagnostic or interventional angiographic procedures; c) all patients had to receive adequate hydration before and after the procedure; d) the primary endpoint had to be the development of CIN, defined as an absolute increase ≥ 0.5mg/dl or a relative increase ≥ 25% in serum creatinine over baseline at 48-72 hours after the angiographic procedure. If both endpoints were reported in a published study, increases of ≥ 25% from baseline were used for the analysis. To standardize the analysis, only data from patients in the placebo or control arm of studies evaluating N-acetylcysteine or other prophylactic measures were considered. Contrast agents having more than one study were evaluated for comparison between the agents by performing pooled analysis for the incidence of CIN.

Bracco noted that nine studies meeting these predefined criteria were identified, two with Omnipaque, three with Visipaque and four with Niopam. A chi-square test was applied to identify any difference among the three contrast agents.

Pairwise comparisons between individual contrast agents were also performed. Data from a total of 560 patients were considered, 245 receiving Niopam, 209 receiving Visipaque and 106 receiving Omnipaque. Similarly to the analysis conducted by Solomon the analysis by Sharma and Kini showed that the pooled incidence of CIN was higher after Omnipaque (25%) compared to Niopam (13.5%) and Visipaque (11%). The results of the pooled analysis showed a significant difference in the occurrence of CIN between Omnipaque and Visipaque ($p = 0.001$) and between Omnipaque and Niopam ($p = 0.024$), while the difference between Niopam and Visipaque was not statistically significant ($p = 0.277$).

Bracco stated that the results of these two pooled analyses of clinical trial data were consistent with the results of a trial comparing Omnipaque, Niopam, and Hexabrix in patients with normal and impaired renal function receiving either intraarterial or intravenous contrast. While no difference in the incidence of CIN was observed in the 228 patients with normal renal function, in the 80 patients with impaired renal function, there was a greater increase in serum creatinine and a trend toward more CIN in the group that received Omnipaque (Campbell *et al* 1990).

In summary, Bracco stated that the available clinical evidence did not show that Visipaque was less nephrotoxic than nonionic monomeric LOCM other than Omnipaque. On the contrary, the incidence of CIN following the administration of Visipaque appeared to be similar to that observed with the LOCM Niopam, Ultravist, and Xenetix in patients at increased risk for CIN. Bracco stated that the available evidence suggested that osmolality played a significant role in the pathogenesis of CIN when it was above 1000mOsm/kg. This was why all existing guidelines recommended that HOCM was not used in patients at increased risk for CIN.

Bracco noted that as far as IOCM or LOCM were concerned, the NEPHRIC study showed a significant difference between Visipaque and Omnipaque, though non-clinical studies and other clinical studies failed to support the benefit of Visipaque over LOCM. This was why the most recent European, American and French guidelines did not support the selective use of IOCM, but recommended the use of either IOCM or LOCM in high risk patients. This was probably why the SPC of Visipaque did not contain any mention about a possible superiority of Visipaque over LOCM with respect to contrast-induced deterioration of renal function in at-risk patients.

Bracco noted the recent review papers of several CIN experts (Thomsen 2005, Morcos 2005, Bettmann 2004, Bettmann 2005, Rudnick 2004, Gleeson and Bulugahapitiya 2004) did not recommend the selective use of IOCM, but to use either IOCM or LOCM in high risk patients.

APPEAL BOARD RULING

The Appeal Board did not accept GE Healthcare's submission that no claim was made that Visipaque was less likely to cause CIN than LOCM. The Appeal Board considered that the claim at issue could not be considered in isolation and would be interpreted in the light of the prominent bar chart beneath which showed that Visipaque, an IOCM, was the only contrast medium with osmolality equal to blood and thus implied that the eight LOCMs and, to a greater extent, the two HOCMs depicted were more likely to induce CIN. In the Appeal Board's view the implied difference in propensity to cause CIN was emphasised by the use of different colours for each group of agents.

The Appeal Board examined all the data provided by GE Healthcare. There was some data to support the claim at issue with regard to the difference between HOCM and IOCM. The data with regard to LOCM was still developing. The Appeal Board considered that whether the osmolality of a contrast medium was an important factor for CIN had not been resolved in favour of one accepted viewpoint with regard to IOCM and LOCM. The Appeal Board considered that the juxtaposition of the claim 'The osmolality of a contrast medium is an important pre-disposing factor for CIN' and the bar chart was misleading and upheld the Panel's ruling of a breach of Clause 7.3. The appeal on this point was unsuccessful.

2 Bar chart entitled 'Osmolality of different contrast media in relation to blood (mOsm/kg H_20)'

This bar chart appeared on page 3 of the leavepiece below the claim at issue in point 1 above.

COMPLAINT

Bracco alleged that it was very unfair to compare Visipaque (270 and 320mgl/ml concentration) to agents at a much higher concentration because the higher the concentration, the higher the osmolality. The osmolality of Iomeprol at 250mgl/ml was 435mOsm/kg and at 300mg/ml was 520mOsm/kg. The graph showed only the osmolality at Iomeprol 350mg/ml (620mOsm/kg), and as such was misleading and in breach of Clauses 7.2 and 7.8 of the Code.

RESPONSE

GE Healthcare noted that the bar chart compared Visipaque at a concentration of 320mg/ml to a range of other contrast media at comparable concentrations and submitted that it was not unfair to make this comparison.

GE Healthcare noted that Bracco's statement 'The higher the concentration, the higher the osmolality' was true for LOCM, but not for the IOCM Visipaque, which had the advantage of being isosmolar to blood at all iodine concentrations. At most clinically relevant concentrations, all LOCM were hyper-osmolar to blood. Although the osmolality of Visipaque was the same as blood at all concentrations, it was clear from the chart that it was the 320mgI/ml concentration of the product that was being compared to its competitors.

GE Healthcare submitted that the leavepiece was aimed at those clinicians who used contrast media in percutaneous coronary angiography with or without

intervention. Its title was, 'How do you manage cardiorenal risk?', and the first page discussed the risks involved in the use of contrast media for PCI. This chart represented the relative osmolalities of different contrast media, at the iodine concentrations most commonly used in this area of practice, 320-370mg/ml.

GE Healthcare submitted that the product information for Iomeron (iomeprol) on Bracco's website recommended various concentrations of the agent for various clinical applications; it was suggested that concentrations of 300, 350 or 400mgI/ml were used for cardiac angiography and intervention procedures. UK market data from 2004 showed that the iodine 350mg/ml concentration of normal Iomeron was most commonly used for this purpose and that was why this concentration was included in the chart, rather than the 300mg/ml or 400mg/ml concentrations.

GE Healthcare noted that Bracco had specifically pointed out the lower (but still significantly higher than blood) osmolality of its iodine 250mg/ml formulation even though this concentration was not indicated for this area of practice (summary of product characteristics (SPC)) and it was therefore inappropriate and misleading to include this concentration in such a comparison. GE Healthcare submitted that for the same reason it did not include its product iohexol at lower concentrations, but showed the iodine 350mg/ml concentration which was more commonly used in this area and had an osmolality in the same range as that of Iomeron at 350mg/ml.

GE Healthcare therefore submitted that this graph reflected accurate information which was highly relevant for the intended audience, was balanced, fair and unambiguous and denied breaches of Clauses 7.2 and 7.8 of the Code.

PANEL RULING

The Panel noted GE Healthcare's submission that the 300, 350 or 400mgl/ml Iomeron concentrations were used for cardiac angiography and intervention procedures.

The bar chart included only data for iodine 350mg/ml Iomeron as this was the most commonly used dose. The Panel did not know whether this was also the selection criteria for all other contrast media listed. The Panel noted that the basis upon which the contrast media had been selected was not clear from the bar chart and thus the comparisons were unfair in this regard. The Panel ruled that this was misleading in breach of Clauses 7.2 and 7.8 of the Code.

The Panel queried whether it was sufficiently clear that the bar chart referred to use in percutaneous coronary angiography and requested that its concerns in this regard be drawn to the attention of GE Healthcare.

APPEAL BY GE HEALTHCARE

GE Healthcare submitted that the bar chart compared Visipaque at an iodine concentration of 320mg/ml to a range of other contrast media at comparable concentrations. At most clinically relevant concentrations, all LOCM were hyper-osmolar to blood. Although the osmolality of Visipaque was the same as blood at all concentrations, it was clear from the chart that it was the 320mgI/ml concentration of Visipaque that was being compared to its competitors.

GE Healthcare submitted that as mentioned above, the leavepiece was specifically designed for, and used exclusively with those clinicians who used contrast media in percutaneous coronary angiography with or without intervention. Its title 'How do you manage cardiorenal risk?' and the first page discussed the risks involved in the use of contrast media for such procedures. This piece had not been used with other customers and was designed to be appropriate for this specific type of customer, who used contrast media for this type of procedure. Supplementary information to Clause 12.1 of the Code stated that promotional material should be tailored to the audience to whom it was directed. This chart represented the relative osmolalities of different contrast media, at the iodine concentrations most commonly used in this area of practice, 320-370mg/ml.

GE Healthcare noted that the core data sheet for Iomeron (iomeprol) recommended iodine concentrations of 300, 350 or 400mgI/ml for cardiac angiography and intervention procedures, and the SPC for the iodine 250mg/ml concentration did not include the indication of cardiac angiography. As previously demonstrated with market data it was the iodine 350mg/ml concentration of Iomeron that was most commonly used for this purpose in the UK and that was why this concentration was included in the chart, rather than the 300mg/ml or 400mg/ml concentrations. Despite this, even if GE Healthcare had included the 300mg/ml concentration of Iomeron, Bracco had stated that the osmolality of this formulation was 520mOsm/kg, which was still significantly higher than the osmolality of Visipaque (290mOsm/kg at 320mg/ml).

GE Healthcare submitted that it would be inappropriate and misleading to include the iodine 250mg/ml formulation of Iomeron in such a comparison as it was not licensed in this clinical area, and for the same reason it did not include its own product iohexol at such lower concentrations, but showed the 350mg/ml concentration that was more commonly used in this clinical area and had an osmolality in the same range as that of Iomeron at 350mg/ml (780 and 620mOsm/kg respectively).

GE Healthcare submitted as appropriate concentrations of contrast media had been compared in this chart, which was directed at and only used with customers who used contrast media primarily for coronary angiography and percutaneous coronary intervention, it considered that this chart reflected accurate information that was highly relevant for the intended audience, that was balanced, fair and unambiguous, and did not breach Clauses 7.2 and 7.8 of the Code.

COMMENTS FROM BRACCO

Bracco referred to its complaint and its comments at point A1 above.

APPEAL BOARD RULING

The Appeal Board considered that its ruling in A1 was relevant here.

The Appeal Board noted GE Healthcare's submission that the iodine 300, 350 or 400mg/ml Iomeron concentrations were used for cardiac angiography and intervention procedures. The bar chart included only data for iodine 350mg/ml Iomeron as this was the most commonly used dose.

The Appeal Board did not know whether this was also the selection criteria for all other contrast media listed. The Appeal Board noted that the basis upon which the contrast media had been selected was not clear from the bar chart and in association with the claim at issue in A1 that the comparisons were unfair in this regard. The Appeal Board ruled that this was misleading and upheld the Panel's ruling of breaches of Clauses 7.2 and 7.8 of the Code. The appeal on this point was unsuccessful.

3 Claim 'Visipaque has less potential for major adverse clinical or cardiac events than the LOCM ioxaglate or iopamidol'

The claim appeared at the top of page 6 beneath the heading 'Contrast the cardiac risk' and above the subheading 'The COURT trial', (Davidson *et al* (2001). Data from the COURT trial followed.

COMPLAINT

Bracco noted that iopamidol was mentioned with ioxaglate in a deliberate attempt to link the results of the COURT trial with iopamidol, which was not included in the trial. This implication was misleading and in breach of Clause 7.2 of the Code.

RESPONSE

GE Healthcare submitted that the claim was clearly referenced to Davidson *et al* (2001) and Harrison *et al* (2003) (the VICC study). Page 6 went on to discuss the COURT trial, which compared Visipaque to ioxaglate, in more detail. The VICC study was a comparison of Visipaque and iopamidol which was supported by Bracco, and showed that the incidence of major adverse cardiac events up to 48 hours post-PCI was significantly reduced in a group of patients who received Visipaque (4.8% incidence) compared to the group that received iopamidol (9%). This study was clearly referenced on page 6. The bar chart was also clearly referenced to the COURT trial and clearly labelled to show it was the result of a study comparing ioxaglate with Visipaque.

GE Healthcare submitted that the information on page 6 was neither misleading nor ambiguous. The company denied a breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that the claim at issue was referenced to Davidson *et al* (The COURT study) and Harrison *et al*. Data from the COURT study was presented. There was no subsequent mention of iopamidol or Harrison *et al*. The Panel considered that the implication was that the COURT study examined the effects of Visipaque, ioxaglate and iopamidol and that was not so. The COURT study did not examine iopamidol. This implication was misleading and a breach of Clause 7.2 of the Code was ruled.

APPEAL BY GE HEALTHCARE

GE Healthcare stated that the claim at issue was clearly referenced to the COURT trial and the VICC trial. These studies demonstrated less major adverse clinical (or cardiac, depending on the terminology used) events with Visipaque than with iopamidol (the VICC trial) or with ioxaglate (the COURT trial). The page went on to discuss the COURT trial which compared Visipaque to ioxaglate in more detail.

GE Healthcare submitted that the VICC trial showed that the incidence of major adverse cardiac events up to 48 hours post-PCI was significantly reduced in a group of patients who received Visipaque compared to the group that received iopamidol (4.8% vs 9% p=0.003). GE Healthcare emphasised that this study was clearly referenced on the page in question. The bar chart was also clearly referenced to the COURT trial and clearly labelled to show it was the result of a study comparing ioxaglate with Visipaque.

GE Healthcare noted that the Panel had ruled that this was misleading in that it implied that the COURT trial examined the effects of Visipaque, ioxaglate and iopamidol. GE Healthcare did not accept that this was the case, as both studies were clearly referenced and the title statement 'Visipaque has less potential for major adverse clinical or cardiac events than the LOCM ioxaglate or iopamidol' was fully supported by the references given. Whilst this statement was referenced to two studies and only one of these studies was subsequently described in more detail, GE Healthcare did not consider that either the letter or the spirit of the Code required companies to give equal weighting, with respect to graphical representation, of all studies referenced in an item, provided that the representation was not misleading. Even if the recipient missed the fact that both studies were clearly referenced which was highly unlikely given the sophisticated scientific backgrounds of these clinicians, they would not be misled with respect to the results of the studies, or with respect to the respective properties of any of the three contrast media. The evidence provided by the two references was clearly reflected and the comparisons made were fair, balanced and unambiguous, therefore it was not in breach of Clause 7.2.

COMMENTS FROM BRACCO

Bracco referred to its original complaint. In addition Bracco strongly disagreed with GE Healthcare's statement that the comparisons made were '… fair, balanced and unambiguous' and alleged that GE Healthcare neglected to report important information, so that the information on page 6 of the leavepiece was misleading.

Bracco noted that as for the potential benefit over Hexabrix (ioxaglate), GE Healthcare did not mention the results of a large multicentre, randomised, double-

blind comparison of Visipaque and ioxaglate, the VIP study, which was larger than the COURT study (856 patients in the COURT trial vs 1411 in the VIP study) and published four months before the COURT study (Bertrand *et al* (2000)). Bracco submitted that the VIP study was very similar to the COURT study. It involved patients undergoing percutaneous coronary intervention. Patients were monitored in the hospital for 2 days and followed-up at 1 month. The primary end point, a composite of major adverse cardiac events (MACE) (death, stroke, myocardial infarction, coronary artery bypass grafting, and re-PTCA) after 2 days, occurred in 4.3% of the total population, with no statistically significant difference between groups (iodixanol, 4.7%; ioxaglate, 3.9%; p=0.45). Further, between 2-day and 1-month follow-up, no significant difference (p=0.27) existed between the groups in the rates of MACE. The only significant predicting factors for the occurrence of MACE were dissection/abrupt closure and country.

Bracco alleged that as for the potential benefit over iopamidol (Niopam), GE Healthcare had mentioned the results of the VICC study contained in a congress abstract. The VICC study had been sponsored by Bracco. MACE was a composite clinical endpoint consisting of either of the following: emergency recatheterisation for documented signs of ischemia, repeat angioplasty, subacute thrombosis/documented abrupt vessel closure, procedure-related Q wave or non-Q wave myocardial infarction, stroke/transient ischemic attack, non-neurological embolic event, emergency coronary bypass surgery, or cardiac death. The main results of the VICC study were:

- A significantly higher rate of non-Q wave myocardial infarctions in the iopamidol group (47 vs 22, $p < 0.05$);
- A significantly higher number of emergency re-catheterization and repeat percutaneous coronary intervention procedures in the Visipaque group (2-7 days post-intervention: 7 vs 18, $p<0.05$).

Bracco noted that Harrison *et al* (2003) clearly reported both results, ie 'Patients undergoing percutaneous coronary intervention using iodixanol had lower in hospital MACE, due to lower rates of non-Q MI following the procedure. The difference in myocardial infarction remained significant at 30 days, although overall 30 day MACE was not different comparing patients receiving iodixanol and iopamidol, due to higher rates of repeat catheterization for ischemia and repeat percutaneous coronary intervention in the iodixanol groups'.

Bracco noted that in the Visipaque leavepiece, GE Healthcare did not report that Visipaque caused a higher number of emergency re-catheterisation procedures for documented signs of ischemia and repeat percutaneous coronary intervention, even if that information was available in Harrison *et al*.

Bracco submitted that the VICC study was fundamentally flawed, since:

- Subjects could have prior diagnostic angiography with non-randomized contrast agents, with no washout period required, so that the majority of patients received more than one agent;
- Laboratory tests, including baseline and post-procedure biomarker tests, were not protocol-mandated, but only documented when obtained on clinical grounds;
- The iopamidol group had sicker patients (more patients with unstable angina, p=0.07);
- The iopamidol group had more patients (27 vs 6) experiencing procedural complications.

Bracco submitted that it had reported the flaws of the VICC study to show how inappropriate it was to use data contained in congress abstracts to support promotional claims. If GE Healthcare wanted to use data from congress abstracts, however, it should at least report all the information contained in those abstracts.

APPEAL BOARD RULING

The Appeal Board noted that the claim at issue compared the adverse clinical effects of two different medicines and cited data from two different studies, Davidson *et al* (the COURT study) and Harrison *et al*. The Appeal Board did not consider that it was unreasonable to cite the references at the end of the claim.

The Appeal Board noted that below the claim at issue data from the COURT study was then presented under the prominent heading 'The COURT trial'. There was no subsequent mention of iopamidol or Harrison *et al*. The Appeal Board did not consider that the claim implied that the COURT study examined the effects of iopamidol. The Appeal Board did not consider that the claim at issue was misleading and ruled no breach of Clause 7.2 of the Code. The appeal on this point was successful.

During its consideration of this matter the Appeal Board was concerned that page 6 might not reflect the balance of available evidence and requested that GE Healthcare be advised of its concerns in this regard.

B Omniscan leavepiece entitled 'delivering confidence'

1 Claim 'Non ionic contrast media generally have low osmolality and are associated with a low rate of adverse reactions'

This appeared on page 4 and was referenced to Chang *et al* (1992).

COMPLAINT

Bracco alleged that the reference cited did not support the claim, Chang *et al* focussed on the correct terminology to define products dissociating in solution from those which did not dissociate. The conclusions were that the terms non-ionic and ionic were appropriate and were indeed the best descriptors of these types of MR imaging contrast enhancing media. This was in breach of Clause 7.6 of the Code.

RESPONSE

GE Healthcare noted that this item had been used from January 2005 by account managers for face-to-

face detailing and as a leavepiece with radiologists (doctors) and radiographers working in the field of magnetic resonance imaging. It had also been used on exhibition stands at meetings in the UK.

The statement 'Non-ionic contrast media generally have low osmolality and are associated with a low rate of adverse reactions' was non-comparative and simply stated that non-ionic contrast media were associated with a low rate of adverse reactions. This statement was supported by the reference given, Chang *et al*. Although GE Healthcare agreed that the main purpose of the reference was to discuss the nomenclature of various contrast types, the first paragraph of the article stated, 'In general, non-ionic radiographic contrast media have low osmolality and have been associated with improved clinical safety profiles'. This was reflected in the statement at the top of page 2 and therefore was not in breach of Clause 7.6 of the Code.

GE Healthcare noted that as ionic compounds dissociated in solution they resulted in a higher number of dissolved particles which in turn resulted in a higher osmolality. This difference in osmolality played an important part in tissue damage when contrast media were accidentally extravasated, a relatively common adverse event. Any difference in adverse events related to differing osmolality was explored on page 4 of the leavepiece, where it compared a non-ionic and an ionic contrast medium and their relative effects on tissue damage after extravasation.

GE Healthcare submitted that Bracco had, in its own promotional material in the past shown the comparative osmolality of various products and stated that the relatively low osmolality of ProHance at a concentration of 1.0M should help to reduce the incidence of adverse events, especially when high doses needed to be administered.

PANEL RULING

The Panel noted that a similar claim to that at issue appeared in the preamble to Chang *et al* and read 'In general, non-ionic radiographic contrast media have low osmolality and have been associated with improved clinical safety profiles'. The statement did not form part of the study conclusions.

The Panel noted that Bracco had alleged a breach of Clause 7.6 of the Code. This clause stated that when promotional material referred to published data clear references needed to be given. The claim did not refer to a published study and thus a reference was not required. Thus there could be no breach of Clause 7.6 of the Code.

2 Bar chart of adverse events

The graph on page 5 compared the retrospectively estimated incidence of adverse events for Omniscan (0.031%), Magnevist (0.067%) and Prohance (0.408%). The differences were not statistically significant. The bar chart was labelled N/S with the explanation 'N/S = not significant' appearing beneath the chart.

COMPLAINT

Bracco alleged that the bar chart was a deliberate attempt to distort the data. The scale was unusual with a range 0 - 0.42 and made the differences between products seem huge although the data was marked non-significant. Secondly, Bracco questioned whether this one study was representative of the general body of evidence, given that the sample sizes for Omniscan were 10x those of the other products. In addition, the adverse events rates were estimated and not measured. For all these reasons, this part of the brochure was in breach of Clause 7.8 of the Code.

RESPONSE

GE Healthcare appreciated that the scale used in the chart had a low percentage (0.42%) as its maximum value, this was due to the very low incidence of adverse events with this type of contrast medium and was exactly the point it was trying to communicate on this page. It would have been impractical and unclear to have tried to portray these data on a scale of 0-100%. Even a scale of 0-1% would have left redundant space above the bars displayed. GE Healthcare did not consider this was misleading. GE Healthcare stated that it did not use an unusual scale in that the scale was linear and clearly labelled, and it was unclear as to what scale Bracco might suggest would be more appropriate.

GE Healthcare submitted that no attempt had been made here to claim any advantage for Omniscan over ProHance or Magnevist. The page on which the chart appeared was clearly headlined 'Omniscan has a low rate of adverse events'. There was no implication that the rate was lower than competitors and the point of the page was to highlight the excellent tolerability of Omniscan and MR contrast media in general. The data for the comparator products were included, as this reflected the findings of the paper from which the data for Omniscan were taken (Murphy *et al* (1999)). Every effort was made to ensure that this chart was not misleading and to make it clear that any differences seen between the products were not statistically significant. The chart was clearly labelled N/S in large font to avoid any possible misinterpretation of the information and its relevance, and the term N/S was explained underneath the chart.

GE Healthcare submitted that because the sample sizes in this study were so large, ranging from 64,000 doses upwards, it did not consider that any discrepancy between the groups detracted at all from the results. Also, GE Healthcare noted that, as stated above, it was not claiming any advantage for Omniscan from this study, as any differences were non-significant as was clearly displayed on the chart. However, the sample sizes for Omniscan were not, as Bracco claimed, ten times higher than the sample sizes of the other products, it was Magnevist that had the highest sample size at over 687,000 doses; Omniscan had 74,275 doses and ProHance 64,005 doses.

Regarding the final point, GE Healthcare accepted that the design of this study was not as robust as a prospective blinded randomised trial and that in using retrospective recall of adverse event rates the

study results could be subject to recall bias. However, the influence of any such bias would have been the same for all the products. This type of retrospective trial would always involve an element of estimation and it was important to point out that whatever the possible weaknesses of such a study, the study was seen as a valid piece of clinical research and accepted by a reputable journal.

Therefore, GE Healthcare denied a breach of Clause 7.8 of the Code.

PANEL RULING

The Panel considered that the presentation of the data with the scale going from 0-0.42 gave the visual impression of a marked difference between the products. This was not so. The differences were not statistically significant. The reference N/S at the top of the bar chart did not negate the misleading impression given. Thus the Panel ruled a breach of Clause 7.8 of the Code.

APPEAL BY GE HEALTHCARE

GE Healthcare noted that the brochure had been used from January 2005 by account managers for face-to-face detailing and as a leavepiece, with radiologists (doctors) and radiographers working in the field of magnetic resonance (MR) imaging. It had also been used on exhibition stands at meetings in the UK.

GE Healthcare noted that the Panel had ruled that the visual impression of a difference between products on this chart was not negated by the results being clearly labelled as not statistically significant. GE Healthcare submitted that the small range covered by the y-axis of this chart was linear and clearly labelled. It resulted from the very low incidence of adverse events with this type of contrast medium which was exactly the point it was trying to communicate on this page. The scale was also entirely consistent with regulatory guidance on the presentation of safety data. A European working group made it clear that marketing authorization holders should present the frequency of adverse event using the following convention: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1,000, <1/100), rare (>1/10,000, <1/1,000), and very rare (<1/10,000). The adverse events at issue here range from rare (>1/10,000, <1/1,000) for Omniscan and Magnevist to uncommon (>1/1,000, <1/100) for ProHance. GE Healthcare submitted that since it was dealing only with data within these ranges, a y-axis within this range was entirely appropriate and could not be considered misleading.

GE Healthcare submitted that not only would it have been inconsistent with the above convention, but it would have been impractical and unclear to have tried to portray these data on a scale of 0-100%. A scale of 0-1% would have left copious redundant space above the bars displayed without altering the readers' understanding and likely impression of the data.

GE Healthcare submitted that every possible effort was made to ensure that this chart was not misleading and to make it clear that any differences seen between the products were not statistically significant. All the products used in this study were included in this chart specifically so as not to suggest that it was only Omniscan which showed an extremely low rate of adverse events. The chart was clearly labelled NS in large font, and to avoid any possible misinterpretation of the information and its relevance, NS was clearly defined underneath the chart.

GE Healthcare noted that the supplementary information to Clause 7.8 of the Code stated that particular care should be taken with such artwork to ensure that it did not mislead, for example by the use of unusual scales. This was not an unusual scale, in that it was clearly labelled and linear. The Code also stated that differences which did not reach statistical significance must not be presented in such a way as to mislead.

GE Healthcare submitted that in this case it had done everything possible in order to portray the results of this study in a clear, fair way which was not misleading. The claim made at the top of the page 'Omniscan has a low rate of adverse events' was not comparative and this was reflected in the chart which accurately portrayed the results of the study; positive results were shown for all three products, including the two products which were competitors to Omniscan. The differences between the groups in this study were not statistically significant, and GE Healthcare had not wished to suggest that there was in fact any difference between groups, but simply that all of these products, including Omniscan, had a remarkably low rate of adverse events.

GE Healthcare did not consider that Clause 7.8 of the Code had been breached.

COMMENTS FROM BRACCO

Bracco referred to its original complaint.

APPEAL BOARD RULING

The Appeal Board considered that the presentation of the data with the scale going from 0-0.42 gave the visual impression of a marked difference between the products. This was not so. The differences were not statistically significant. The reference N/S at the top of the bar chart did not negate the misleading impression given. Thus 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.

3 Data from animal studies

A bar chart on page 6 presented data related to tissue histopathology after injecting mice.

COMPLAINT

Bracco noted that the data was from animal studies injecting contrast sub-cutaneously. This was outside the product licence and thus the relevance had to be questioned. Bracco alleged a breach of Clause 7.2 of the Code.

RESPONSE

GE Healthcare noted that Runge *et al* (2002) was designed to compare the relative toxicities of MR contrast agents when extravasated in soft tissue. Extravasation was a relatively common, unintended consequence of the use of intravascular contrast media. As contrast media were not intended to be injected under the skin of either mice or humans, this study was not technically within the licences of any of these products. However, as extravasation did occur in clinical practice, sometimes with unpleasant consequences for the patient, this issue was clearly relevant to the promotion of contrast media.

GE Healthcare submitted that such a study in human patients would be considered unethical, and so the use of an animal model was unavoidable here. It was made very clear that this study was in mice, and the intended recipient could not be misled by these data. GE Healthcare therefore did not believe that Clause 7.2 of the Code had been breached.

GE Healthcare submitted that in previous promotional material where Bracco had claimed that its product's low osmolality reduced complications associated with extravasation, it had actually referenced the very same paper, without mentioning that the study was performed in animals. GE Healthcare submitted that as this was an item from the USA it was not initiating a complaint about this not being clearly indicated as an animal study, but nevertheless, it was surprised at this aspect of the complaint.

GE Healthcare submitted that it was also possible to find its counter-arguments to Bracco's complaint summarised very succinctly on its own web site: http://www.bracco.com/Bracco/Internet/Services/Medical+Profession+Services/Folder/Extravasations.htm. Bracco quoted:

'Extravasations of contrast media, usually involving an iodinated agent power-injected during CT scanning, but possibly involving a gadolinium agent injected during dynamic MR scanning, occur not infrequently, and can be a cause of medical concern.

If an extravasation does occur while you are injecting a contrast agent, please keep the following in mind:

a) Contrast agent manufacturers are not health care providers, and cannot provide medical advice about patient treatment.

b) There is no 'antidote', as such, to contrast media. The effects of contrast media on tissue are not caused by iodine, or gadolinium, or some other chemical factor peculiar to these agents, but instead by their general chemical characteristics of osmolality and ionicity, and by physical factors such as the volume extravasated, and where the extravasation occurred.

c) Hyperosmolar ionic contrast media are far more likely to cause skin necrosis, skin ulceration or compartment syndrome than low osmolar nonionic media; however, ill effects are not impossible with low osmolar nonionic agents.

d) Authors differ widely in how to treat extravasations; there is no one right answer, and of course there cannot be a randomized clinical trial to find such an answer, as it would be quite unethical to deliberately produce extravasations in human subjects.'

PANEL RULING

The Panel noted that the animal data appeared as part of a double page spread which clearly referred to the use of the product in humans. Details of licensed dosages appeared before the animal data which was followed by examples of scans of patients.

The Panel accepted that it would not be possible to carry out a clinical trial to confirm the results obtained in mice. The Panel was unsure of the relevance of the animal data to the clinical situation.

The Panel considered that the presentation of the animal data was misleading. It was not sufficiently clear that the data were from mice reference to which appeared in small print adjacent to the bar chart. The relevance to the clinical situation was questionable. A breach of Clause 7.2 of the Code was ruled.

APPEAL BY GE HEALTHCARE

GE Healthcare noted that Clause 7.2 of the Code stated that care must be taken with data derived from studies in animals, so as not to mislead to their significance. The extrapolation of such data to the clinical situation should be made only where there was data to show that they were of direct relevance and significance.

GE Healthcare submitted that Runge *et al* was a frequently cited study and had also been used in promotional material produced by Bracco. The study compared the relative toxicities of magnetic resonance contrast agents when extravasated in soft tissue. As extravasation was a relatively common although unintended consequence of the use of intravascular contrast media which could have unpleasant consequences for the patient, this issue was clearly relevant to the safety aspects of the use of contrast media. An extravasation study in patients would be considered unethical, and so the use of an animal model to examine the issues was unavoidable.

Elam *et al* (1991) identified a definitive animal model for assessing cutaneous toxicity due to contrast extravasation, and used intradermal injections in a strain of mouse previously used successfully as a model for evaluating the cutaneous toxicity of chemotherapeutic agents. The authors concluded that the mouse was an effective model for studying hyperosmolar contrast injuries of the skin. Although the findings could not be definitively extrapolated to the clinical situation, the authors suggested they might have important implications for selection of contrast materials and management of cases of accidental extravasation in humans. Such mouse studies thus appeared to be the best model for studying contrast extravasation injuries and therefore it was appropriate to use Runge *et al* in discussion of the safety of contrast media provided that it was clearly stated that the study was performed in mice.

GE Healthcare submitted that it was aware that this study was presented on a page which also discussed

studies in humans, however it did not accept that that this was done in a misleading way; the page was clear that these data were not from a study in humans. Whilst it would have been possible to increase the font size of the statement 'Tissue histopathology after subcutaneous injection of contrast media in mice', it was not necessary to do this as the existing font was sufficiently large and prominent that this statement was not likely to be missed by the intended recipient, the MR specialist who was used to reading clinical papers and other such materials in detail. In fact, the intended recipient would not even think that a study like this would be conducted in any other than an animal model. Accordingly, GE Healthcare did not accept that the intended recipient could be misled by these data and denied a breach of Clause 7.2 of the Code.

COMMENTS FROM BRACCO

Bracco referred to its original complaint.

APPEAL BOARD RULING

The Appeal Board noted that extravasation data would be of interest to health professionals. Although the Appeal Board accepted that it would not be ethical to conduct a clinical trial on the effects of extravasation, the relevance of the animal data to patients was not clear. GE Healthcare did not provide any observational data from accidental extravasation of contrast media to show that the data in mice echoed what might be observed in patients.

The Appeal Board considered that it was not sufficiently clear that the data at issue came from mice. The Appeal Board considered that the claim 'Non-ionic Omniscan can cause less tissue damage than ionic Magnevist' implied that a difference between the two agents in favour of Omniscan had been proven. This was not so. Overall the Appeal Board considered that the presentation of the data was misleading as alleged. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2 of the Code. The appeal on this point was unsuccessful.

4 Packaging formats

COMPLAINT

Bracco noted that on page 8 there was a claim of a 'wide range of packaging formats' whereas two formats were displayed. This was an exaggeration and in breach of Clause 7.10 of the Code.

RESPONSE

GE Healthcare submitted that Omniscan was available in a wide range of packaging formats was clear on page 8. Although as Bracco had commented there were only two product presentations pictured, the polypropylene bottle was available in different volumes, as shown. This pack range was important to the departments that used contrast media as it allowed the appropriate format to be chosen depending on the number and type of procedures planned. Therefore GE Healthcare submitted that this was not an exaggerated claim nor that it was in breach of Clause 7.10 of the Code.

PANEL RULING

The Panel considered that as presented it was misleading and exaggerated to illustrate a claim that Omniscan delivered a wide range of packaging formats for flexibility and ease of use with a picture of two packaging formats, a glass vial and a soft pack. A breach of Clause 7.10 of the Code was ruled.

Complaint received	**14 July 2005**
Case completed	**29 November 2005**

CASE AUTH/1745/7/05

ANONYMOUS v ABBOTT

Arrangements for meetings

An anonymous complaint was received about a number of meetings held by Abbott Laboratories.

The complainant alleged that in January 2004 and September 2004 named managers approved two meetings at a greyhound stadium in Manchester for hospital doctors and that greyhound racing was in progress at the time of the meetings.

The Panel noted that twenty-seven health professionals had attended the meeting in January and thirty-six had been present in September and that greyhound racing had taken place on both evenings. Abbott stated that it was unable to provide a full picture of what had occurred at these meetings. The Panel considered that it was unacceptable that health professionals had been taken to a restaurant at a greyhound stadium on two evenings and the company had no record of what the meetings were about nor a complete record of attendees. The Panel considered it highly likely that the meetings were mainly of a social or sporting nature which was unacceptable under the Code.

The fact that only limited evidence was available was primarily due to Abbott's inability to provide adequate information about events for which it had to take responsibility. Companies must maintain adequate records. High standards had not been maintained either by the company or the representative. Breaches of the Code were ruled. The meetings were such as to bring discredit upon, and reduce confidence in, the pharmaceutical industry and a breach of Clause 2 was ruled.

The complainant alleged that in early 2004 a senior manager authorised for a health professional to be taken to a lap dancing club.

The Panel noted that the two Abbott employees involved had attended a workshop during the course of their employment – one as a delegate and the other to man a promotional stand. After the workshop dinner the two employees had gone, with a health professional, who was involved in the organisation of the workshop, to a lap dancing club. The Panel considered that although this activity was not approved by the company nor paid for by the company, it was nonetheless related to the manager's and representative's employment given that a health professional, a potential customer, was involved. The professional interests of all three had presumably caused them to meet. High standards had not been maintained. Breaches of the Code were ruled. The Panel considered that irrespective of whether company money had been used to fund the visit to the nightclub, such activity would bring discredit upon, and reduce confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

The complainant alleged that a senior manager had invited senior hospital consultants to Wimbledon; this involved centre court tickets and full hospitality.

The Panel noted that corporate events were a legitimate business activity. Whether a corporate event was subject to the Code would depend on the arrangements. In order to be exempt from the Code corporate events must not otherwise be meetings organised for health professionals or appropriate administrative staff, bearing in mind that meetings organised for such groups which were wholly or mainly of a social or sporting nature, were unacceptable. Further, inviting health professionals in their capacity as prescribers to a corporate event with no educational or scientific input would be a breach of the Code.

The Panel ruled breaches of the Code in relation to the social nature of the meeting and as high standards had not been maintained. The arrangements brought discredit upon, and reduced confidence in, the pharmaceutical industry and a breach of Clause 2 was ruled.

The complainant alleged that the partners of two Abbott employees attended all national and international meetings in a particular therapy area and asked if this was preferential biased treatment.

The Panel noted that there was no evidence that either doctor had received preferential treatment from Abbott. Both doctors might be appropriate delegates to any meeting in their particular therapy area. The Panel ruled no breach of the Code.

The complainant alleged that in December 2004 an evening meeting had been held at a named restaurant for approximately fifteen people; there had been no medical content and the bill was over £800.

The Panel ruled breaches of the Code as the meeting was a social event, a hospital department's Christmas dinner and high standards had not been maintained. The Panel considered that the arrangements brought discredit upon, and reduced confidence in, the pharmaceutical industry and a breach of Clause 2 was ruled.

The Panel was concerned about what had occurred in relation to the allegations ruled in breach of the Code. A serious allegation had been made about greyhound racing but the company had been unable to satisfactorily respond. The events ruled in breach were unacceptable and each had been ruled in breach of Clause 2. They were very serious matters. In accordance with Paragraph 8.2 of the Constitution and Procedure, the Panel decided that these matters warranted reporting Abbott to the Appeal Board for it to consider them in relation to Paragraphs 10.4 and 12.1 of the Constitution and Procedure.

The Appeal Board noted that Abbott was aware of the problems that had existed within the company before the complaint had been made to the Authority. When Abbott was informed of the complaint by the Authority it had already undertaken a major investigation of events and a review of its procedures. The company had acted promptly in that regard. Nonetheless, the

allegations were extremely serious and Abbott had accepted rulings of breaches of the Code.

The Appeal Board decided that Abbott should undergo an audit of its procedures in accordance with Paragraph 10.4 of the Constitution and Procedure. The Appeal Board also decided to report Abbott to the ABPI Board of Management in accordance with Paragraph 12.1 of the Constitution and Procedure.

The ABPI Board noted that Abbott had been ruled in breach of the Code and that the breaches were so serious as to also involve breaches of Clause 2. Abbott had given the requisite undertaking in respect of these breaches. In mitigation Abbott submitted that these activities were due to the actions of specific individuals for whom responsibility was accepted and that the company culture was sound. Some members of the ABPI Board considered that due to the number of persons involved, albeit relatively few, and their positions within the company it might be too early to pronounce on the soundness of culture.

The ABPI Board noted the audit report and Abbott's comments upon it.

The ABPI Board appreciated that the current management was taking action to avoid recurrence in the future and was encouraged in that regard; however, in considering appropriate sanctions the ABPI Board noted that this was one of the most serious cases it had considered. It decided that in this instance a corrective statement would not be appropriate and that a public reprimand would not reflect the seriousness of the circumstances. The ABPI Board thus decided to suspend Abbott from membership of the ABPI for a minimum of six months, commencing 1 January 2006. In addition the ABPI Board required an audit of Abbott's procedures in relation to the Code. This audit would take place in May 2006 and would be used to assess whether the requirements for improvement laid down in the audit of November 2005 had been satisfactorily implemented.

An anonymous 'concerned member of the industry' complained about a number of meetings which Abbott Laboratories Limited had held over recent years. The complainant alleged breaches of Clauses 2, 15.3, 15.4, 16.1, 18 and 19 of the Code. In addition to those clauses, the Authority asked Abbott to consider the requirements of Clauses 9.1 and 15.2.

Abbott stated that during an internal investigation of unrelated activities complaints had been made. A number of these allegations were repeated in this complaint. These allegations had been thoroughly investigated. Following this investigation two managers and one additional employee had left the company.

1 Meetings at a greyhound stadium

COMPLAINT

The complainant alleged that in January 2004 and September 2004 named managers approved two meetings at a greyhound stadium in Manchester for hospital doctors and that greyhound racing was in progress at the time of the meetings.

RESPONSE

Abbott stated that as these meetings did not include overnight accommodation, hospitality over £40 per head or £2000 in total, they were not required to be approved via head office. Therefore the only evidence available was from the territory management system and expenses claims. These showed:

a) January 2004

'Multidisciplinary hospital meeting' held for twenty-seven customers (nine named health professionals and eighteen other health professionals) with a bill for £419.27 for 'meals and drinks', ie £14.98 per head. The only Abbott employee present was a representative.

b) September 2004

'Multidisciplinary hospital meeting' held for thirty-six customers (thirteen named health professionals and twenty-three other health professionals). The bill was £450 ie £12.16 per head. The only Abbott employee present was a representative.

There were no further details available to confirm the content of the meetings and no evidence that standard pre-approval invitations were sent out.

The representative who organised these meetings and the line manager had left the company. The sales manager had previously left the company, but had no recollection of these meetings.

Abbott stated that from the evidence available it was not possible to confirm a full picture of what occurred at these meetings.

In response to a request for further information Abbott explained that the line manager who would have approved this meeting had left the company. The line manager had been trained in the company's standard operating procedure and the Code. Only the representative's immediate line manager would have had to approve meetings of this value in advance. That line manager would also have had to approve any claims for reimbursement, which were then reviewed by head office finance staff prior to payment.

PANEL RULING

The Panel noted that in response to the request for further specific information Abbott had not provided any further details as to the content of the meeting nor had it confirmed whether greyhound racing had taken place at the same time.

The Panel noted that two meetings had been held at the greyhound stadium. Twenty-seven health professionals had attended the meeting in January and thirty-six had been present in September. The Internet showed that greyhound racing had taken place on both evenings. Abbott stated that it was unable to provide a full picture of what had occurred at these meetings. The Panel considered that this was

unacceptable; sixty-three health professionals had been taken to a restaurant at a greyhound stadium on two evenings and the company had no record of what the meetings were about nor a complete record of attendees. Given the atmosphere that must prevail in a stadium restaurant on a race night the Panel considered it highly likely that the meetings were mainly of a social or sporting nature which was unacceptable under the Code.

The fact that only limited evidence was available was primarily due to Abbott's inability to provide adequate information about events for which it had to take responsibility. Companies must maintain adequate records. The Panel considered that it was unacceptable for a company to offer its own lack of records as a response to an allegation that it had breached the Code. High standards had not been maintained either by the company or the representative. Breaches of Clauses 9.1 and 15.2 of the Code were ruled. The meetings were not in accordance with Clause 19 of the Code and were such as to bring discredit upon, and reduce confidence in, the pharmaceutical industry. Breaches of Clauses 2 and 19.1 were ruled.

2 Hospitality at a lap dancing club

COMPLAINT

The complainant alleged that in February 2004 a named senior manager authorised for a hospital doctor to be taken to a lap dancing club to be entertained. The complainant made allegations in relation to the nature and cost of the entertainment. The complainant stated that the manager borrowed £1,000 from the local representative towards the evening informing him that he would be fully reimbursed, however this never materialised and he was still waiting for his money.

RESPONSE

Abbott confirmed that two members of its staff (a manager and a representative) attended a lap dancing club with the doctor. This took place after dinner during a two day workshop. The manager was present at the meeting as a delegate, the representative was there to man a promotional stand. The doctor was not a guest of Abbott and the Abbott employees sought no approval nor any monies from Abbott in connection with their activities that evening after dinner.

As this activity took place in their own time and at their own expense, it was Abbott's view that this was outside of the scope of their employment and therefore outside the remit of the Code. However, this behaviour was inconsistent with Abbott's code of conduct; these individuals had left the company.

PANEL RULING

The Panel noted that the two Abbott employees had attended a workshop during the course of their employment with Abbott – one as a delegate and the other to man a promotional stand. After the workshop dinner the two employees had gone, with a health professional who was involved in organising the workshop, to a lap dancing club. The Panel considered that although this activity was not approved by the company nor paid for by the company it was nonetheless related to the manager's and representative's employment given that a health professional, a potential customer, was involved. The professional interests of all three had presumably caused them to meet. High standards had not been maintained. Breaches of Clauses 9.1 and 15.2 were ruled. The Panel considered that irrespective of whether company money had been used to fund the visit to the nightclub such activity would bring discredit upon, and reduce confidence in, the pharmaceutical industry. A breach of Clause 2 of the Code was ruled.

3 Hospitality at Wimbledon

COMPLAINT

The complainant alleged that in the summer of 2004 a senior manager had invited senior hospital consultants from London to Wimbledon; this involved centre court tickets and full hospitality.

RESPONSE

Abbott confirmed that a previous general manager of the company had asked another manager to invite a number of senior consultants to corporate hospitality at Wimbledon. They were personal invitations from the previous general manager that were not reviewed via Abbott's Code of Practice review procedures. The company's understanding of what was acceptable with regard to corporate hospitality had changed following Case AUTH/1604/7/04.

Abbott accepted a breach of Clause 19.1. The new general manager [in place from December 2004] had undertaken that should there be any future invitations to corporate events the medical division signatories for compliance with the Code should review them.

PANEL RULING

The Panel noted that corporate events were a legitimate business activity. Whether a corporate event was subject to the Code would depend on the arrangements. In order to be exempt from the Code corporate events must not otherwise be meetings organised for health professionals or appropriate administrative staff, bearing in mind that under the supplementary information to Clause 19.1, meetings organised for such groups which were wholly or mainly of a social or sporting nature, were unacceptable. Further, inviting health professionals in their capacity as prescribers to a corporate event with no educational or scientific input would be a breach of the Code.

The Panel ruled a breach of Clause 19.1 of the Code which it noted had been accepted by Abbott. High standards had not been maintained and a breach of Clause 9.1 was ruled. The arrangements brought discredit upon, and reduced confidence in, the pharmaceutical industry and a breach of Clause 2 was ruled.

4 Alleged preferential treatment of two health professionals

COMPLAINT

The complainant alleged that the partners of two Abbott employees attended all national and international meetings in a particular therapy area and asked if this was classed as overkill or preferential biased treatment.

RESPONSE

Abbott stated that the complaint was factually inaccurate in that one of the named employees was not in a relationship as stated by the complainant. As senior specialist physicians in their field, both doctors were appropriate recipients of sponsorship. They had not been invited to all national and international meetings as alleged. A schedule of meetings (including the costs incurred) attended by the doctors was provided.

PANEL RULING

The Panel noted that there was no evidence that either doctor had received preferential treatment from Abbott. Both doctors were senior physicians and might be appropriate delegates to any meeting in their particular therapy area. The Panel ruled no breach of Clause 18.1 of the Code.

5 Meeting at a restaurant

COMPLAINT

The complainant alleged that in December 2004 a meeting had been held at a named restaurant for approximately 15 people; there had been no medical content and the bill was over £800. The complainant alleged that two managers had arrived one and a half hours late and were intoxicated.

RESPONSE

Abbott explained that this meeting was in effect the Christmas dinner for a department of a named hospital sponsored at a customer's request and did not constitute acceptable hospitality and was in breach of Clause 19.1.

This meeting was paid for by one manager and approved by another. Both of these individuals had received training on the Code from Abbott and were therefore fully aware of their responsibilities and Abbott's meeting policies, and thus in breach of Clause 15.2. Both were no longer with the company.

The bill was £783.73 which worked out at £32.66 per head.

The allegation that two managers arrived late and intoxicated was denied by the individuals. They insisted that the customers present would support their assertions if asked; Abbott considered it inappropriate to do so.

The marketing process covering these individuals' work dictated that any meeting costing over £100 required prior approval, including compliance with the Code, by the representative's line manager, via the computerised territory management system; without approval reimbursement of cost could not take place.

Abbott provided copies of its meetings procedures in force at the time, the relevant training package on the Code and an example of the training slides used during recent field force training.

PANEL RULING

The Panel noted that the meeting was a social event – it was a hospital department's Christmas dinner. A breach of Clause 19.1 was ruled which had been acknowledged by Abbott. High standards had not been maintained and breaches of Clauses 9.1 and 15.2 were ruled (Abbott had acknowledged the breach of Clause 15.2). The Panel considered that the arrangements brought discredit upon, and reduced confidence in, the pharmaceutical industry and a breach of Clause 2 of the Code was ruled.

* * * * *

The Panel was concerned about what had occurred in relation to points 1, 2, 3 and 5 above. A serious allegation had been made at point 1 but the company had been unable to satisfactorily respond. The events at points 2, 3 and 5 were unacceptable and each had been ruled in breach of Clause 2. They were very serious matters. In accordance with Paragraph 8.2 of the Constitution and Procedure, the Panel decided that these matters warranted reporting Abbott to the Appeal Board for it to consider them in relation to Paragraphs 10.4 and 12.1 of the Constitution and Procedure.

COMMENTS FROM ABBOTT

Abbott submitted that it recognised the seriousness of the Panel's rulings; the company emphasised that the findings represented the action of a small minority, rather than cultural or process deficiency. Abbott submitted that its processes were sound and that the staff in its organisation were aware of their ethical responsibilities.

In all but one of these cases a narrow silo in the organisation had exposed themselves and Abbott to environments and circumstances that failed to uphold the standards of the company or the industry. Abbott explained the organisation, management lines and investigations relevant to the rulings, whilst recognising the company's responsibility with regard to the activities of its employees.

At the report hearing, the Abbott representatives stated that they accepted the Panel's rulings of breaches of the Code. The company explained the circumstances that had given rise to the complaint. As a result of its investigations Abbott had, inter alia, changed the structure of one of its business units and reviewed its meetings processes and procedures. The events occurred in 2004; the new UK general manager joined in December 2004. Two managers and one additional employee had left the company.

APPEAL BOARD CONSIDERATION

The Appeal Board noted that Abbott was aware of the problems that had existed within the company before the complaint had been made to the Authority. When Abbott was informed of the complaint by the Authority it had already undertaken a major investigation of events and review of its procedures. The company had acted promptly in that regard. Nonetheless, the allegations were extremely serious and Abbott had accepted rulings of breaches of the Code.

The Appeal Board decided that Abbott should undergo an audit, within the next month, of its procedures in accordance with Paragraph 10.4 of the Constitution and Procedure. The Appeal Board also decided to report Abbott to the ABPI Board of Management in accordance with Paragraph 12.1 of the Constitution and Procedure. To expedite matters, the Appeal Board requested that the audit report be sent to both it and the ABPI Board.

ABPI BOARD OF MANAGEMENT CONSIDERATION

The ABPI Board noted that Abbott had been in breach of Clauses 9.1, 15.2 and 19.1 of the Code and that the breaches were so serious as to also involve breaches of Clause 2. It also noted the audit report and Abbott's comments upon it.

Abbott had given the requisite undertaking in respect of these breaches. In mitigation Abbott submitted that these activities were due to the actions of specific individuals for whom responsibility was accepted and that the company culture was sound. Some members of the ABPI Board considered that due to the number of persons involved, albeit relatively few, and their positions within the company it might be too early to pronounce on the soundness of culture.

The ABPI Board appreciated that the current management was taking action to avoid recurrence in the future; however, in considering appropriate sanctions the ABPI Board noted that this was one of the most serious cases it had considered. It decided that in this instance a corrective statement would not be appropriate and that a public reprimand would not reflect the seriousness of the circumstances. The ABPI Board thus decided to suspend Abbott from membership of the ABPI for a minimum of six months. In addition the ABPI Board required an audit of Abbott's procedures in relation to the Code. This audit would take place in May 2006 and would be used to assess whether the requirements for improvement laid down in the audit of November 2005 had been satisfactorily implemented.

The ABPI Board was encouraged by the action being taken by the current management but, in view of the gravity of this case, suspension was nonetheless considered to be an appropriate sanction.

The suspension would take effect from 1 January 2006 and the minimum six month period would end on 30 June 2006.

Complaint received	**22 July 2005**
PMCPA Proceedings completed	**19 October 2005**
ABPI Board consideration	**5 December 2005**

CASE AUTH/1753/8/05

BRISTOL-MYERS SQUIBB and OTSUKA/DIRECTOR v LILLY

Zyprexa leavepiece

Bristol-Myers Squibb and Otsuka jointly complained about a leavepiece issued by Lilly which comprised a folder entitled 'Case Study "A Meta-Analysis of the Efficacy of Second Generation Antipsychotics"', and contained a reprint of Davis *et al* (2003), a critical appraisal form for a meta-analysis and a two-page structured summary of Davis *et al*. As the complaint included an alleged breach of undertaking that aspect of the complaint was taken up by the Director as the Authority was responsible for ensuring compliance with undertakings. This accorded with advice previously given by the Appeal Board.

Bristol-Myers Squibb and Otsuka explained that the leavepiece in question was made freely available on a Lilly exhibition stand at an educational meeting. Davis *et al* and its use in another leavepiece by Lilly had previously been ruled in breach of the Code (Case AUTH/1634/9/04).

Since that case it had become apparent that Lilly was continuing to refer to Davis *et al* in the leavepiece now at issue which summarised the authors' main findings including definitive statements about the relative efficacy of aripiprazole. In particular:

- **'Efficacy differences:**

Other SGAs [second generation antipsychotics] (e.g. quetiapine, aripiprazole) were NOT significantly different from FGAs [first generation antipsychotics] …

The rest of SGAs – e.g. quetiapine, aripiprazole (SIMILAR efficacy to that of FGAs).'

For identical reasons to those in Case AUTH/1634/9/04, Bristol Myers Squibb and Otsuka alleged that the continued representation of these data in this way constituted a further breach of the Code. The Appeal Board had previously ruled that the table of data at issue implied that Davis *et al* had unequivocally demonstrated that aripiprazole and haloperidol were equivalent in terms of efficacy and this was not so. In its consideration the Panel had noted that later data (Kasper *et al* 2003) had shown that aripiprazole was at least as effective as haloperidol.

The complainants' view was that athough the leavepiece now at issue did not contain a table of the meta-analysis findings, it nevertheless stated, unequivocally, that the efficacy of aripiprazole was not significantly different to that of FGAs (a group which included haloperidol). There had been no attempt to place the findings in the context stated by Davis *et al*, namely 'Failure to find a statistically significant difference does not prove that these drugs are equal to [first generation antipsychotics] because there is a possibility that further studies could demonstrate this'.

In view of this continued misrepresentation of Davis *et al* and the same distortion of data previously ruled in breach, Bristol-Myers Squibb and Otsuka alleged breaches of the Code.

The Panel noted that the previous case, Case AUTH/1634/9/04 concerned, *inter alia*, a table of data which listed those antipsychotics which were significantly better than haloperidol and those antipsychotics which were equivalent to haloperidol (including, *inter alia*, aripiprazole). The Appeal Board had upheld the Panel's ruling of breaches of the Code as it considered that the table of data was too simplistic; it implied that Davis *et al* had unequivocally demonstrated that haloperidol and aripiprazole were equivalent in terms of effectiveness, and that was not so.

Turning to the case now before it (Case AUTH/1753/8/05) the Panel considered that the two page structured summary of Davis *et al* provided in the folder with the entire paper was sufficiently different in format and content to the material at issue previously (Case AUTH/1634/9/04) such that it was not caught by the undertaking given in that case. No breaches of the Code, including Clause 2, were thus ruled.

The Panel considered that its comments in the previous case about Davis *et al* were relevant to the present case. Davis *et al* reviewed 142 controlled studies, however not all of the medicines were equally represented. For example 31 studies involving clozapine were included in the meta-analysis vs three for aripiprazole. The data was thus more compelling that there was an advantage for clozapine vs haloperidol as opposed to the equivalence of haloperidol and aripiprazole. Davis *et al* stated that 'Failure to find a statistically significant difference does not prove that these drugs are equal to [first generation antipsychotics] because there is a possibility that further studies could demonstrate this'.

The Panel noted that the structured summary at issue in the current case set out the background, objectives, methods and main findings of Davis *et al*. Some statements in the main findings section were emphasised by the use of upper case text. The first bullet point in this section described the effect sizes and p values of olanzapine, amisulpride, risperidone and olanzapine compared to FGAs as 'HIGHLY STATISTICALLY SIGNIFICANT – the best evidence of difference'. A subsequent bullet point began 'THREE EFFICACY GROUPS OF SGA have been established'. This was followed by 'Other SGAs (e.g. quetiapine, aripiprazole) were NOT significantly different from FGAs' beneath which the third bullet point read 'The rest of SGAs – e.g. quetiapine, aripiprazole (SIMILAR efficacy to that of FGAs)…'. There was no claim that aripiprazole had equivalent efficacy to haloperidol, the terms 'similar' and 'not statistically significant' had been used. The Panel considered, however, that the section implied that Davis *et al* had been unequivocal on this point and that was not so. The use of upper case text compounded the misleading impression given. A breach of the Code was ruled.

Bristol-Myers Squibb Pharmaceuticals Limited and Otsuka Pharmaceuticals (UK) Limited jointly complained about a leavepiece (ref ZY2552) issued by Eli Lilly & Company Limited. The leavepiece comprised a folder entitled 'Case Study "A Meta-Analysis of the Efficacy of Second Generation Antipsychotics"', which contained a reprint of Davis *et al* (2003), a critical appraisal form for a meta-analysis and a two-page structured summary of Davis *et al*. As the complaint included an alleged breach of undertaking that aspect of the complaint was taken up by the Director as the Authority was responsible for ensuring compliance with undertakings. This accorded with advice given by the Appeal Board.

Lilly marketed Zyprexa (olanzapine) and Bristol-Myers Squibb and Otsuka jointly marketed Abilify (aripiprazole). Both products were antipsychotics.

COMPLAINT

Bristol-Myers Squibb and Otsuka explained that the leavepiece was made freely available on a Lilly exhibition stand at an educational meeting about perinatal psychiatry held in July 2005. Davis *et al* and its use in an associated leavepiece by Lilly, was the subject of a complaint and subsequent Appeal Board ruling (Case AUTH/1634/9/04). Lilly was unsuccessful in its appeal and ruled in breach of Clauses 7.2 and 7.3, therefore requiring withdrawal of the material.

Since that case it had become apparent that Lilly was continuing to refer to Davis *et al* in the leavepiece at issue which summarised the authors' main findings including definitive statements about the relative efficacy of aripiprazole. In particular:

- 'Efficacy differences:
Other SGAs [second generation antipsychotics] (e.g. quetiapine, aripiprazole) were NOT significantly different from FGAs [first generation antipsychotics] …

The rest of SGAs – e.g. quetiapine, aripiprazole (SIMILAR efficacy to that of FGAs).'

For identical reasons to those in Case AUTH/1634/9/04, Bristol Myers Squibb and Otsuka alleged that the continued representation of these data in this way constituted a further breach of Clause 7.2. With regard to this particular issue, the Appeal Board had previously ruled that the table of data at issue implied that Davis *et al* had unequivocally demonstrated that aripiprazole and haloperidol were equivalent in terms of efficacy and this was not so. In its consideration the Panel had further noted that later data (Kasper *et al* 2003) had shown that aripiprazole was at least as effective as haloperidol.

Although the leavepiece now at issue did not contain a table of the meta-analysis findings, it nevertheless stated, unequivocally, that the efficacy of aripiprazole was not significantly different to that of FGAs (a group which included haloperidol). There had been no attempt in the leavepiece to place the findings in the context stated by Davis *et al*, namely 'Failure to find a statistically significant difference does not prove that these drugs are equal to [first generation antipsychotics] because there is a possibility that further studies could demonstrate this'.

In view of this continued misrepresentation of the findings of Davis *et al*, Bristol-Myers Squibb and Otsuka alleged a breach of Clause 7.2 of the Code. Furthermore, in light of the previous ruling and the persistent use of the same distortion of data thereafter which was contrary to Paragraph 7.1 of the Constitution and Procedure ('… all possible steps will be taken to avoid a similar breach of the Code in the future'), Bristol-Myers Squibb and Otsuka alleged breaches of Clauses 2, 9.1 and 22 of the Code.

RESPONSE

Lilly explained that it was found in breach of the Code in Case AUTH/1634/9/04 in relation to a table which presented data from Davis *et al*. The table had listed those antipsychotics, including olanzapine, which were significantly better than haloperidol and those including aripiprazole, which were equivalent to haloperidol. Although Davis *et al* concluded that no statistically significant difference was found between aripiprazole and haloperidol, the Panel ruled that the table of data 'implied that Davis *et al* had unequivocally demonstrated that aripiprazole and haloperidol were equivalent in terms of efficacy'. The Panel thus considered that the table of data was misleading. On appeal the Appeal Board upheld the Panel's ruling. 'The Appeal Board considered that the table of data at issue was too simplistic: it implied that Davis *et al* had unequivocally demonstrated that aripiprazole and haloperidol were equivalent …'. Neither the Panel nor the Appeal Board made any specific ruling relating to non-usage of Davis *et al*. There was no undertaking that related to specific non-use of Davis *et al*. Lilly gave an undertaking that the leavepiece in question and any similar material would be discontinued forthwith. In addition Lilly gave an assurance that it would take all possible steps to avoid similar breaches occurring in the future.

The leavepiece now at issue was a folder which contained three items; a reprint of Davis *et al*, a four-sided form for the purpose of critically appraising a meta-analysis (adapted from material produced by the Centre for Evidence-Based Mental Health at the University of Oxford) and a structured summary of Davis *et al*. Each item was labelled with the same reference number ZY2552 to ensure that the folder was a single promotional item. The purpose of the folder was to provide a clinical paper suitable for doctors to undertake a critical appraisal – an exercise that was an integral part of the MRCPsych examination. The complete clinical paper would have to be read to perform this task.

Lilly considered that the continued usage of the leavepiece at issue, which was first used in November 2004 and not withdrawn following completion of Case AUTH/1634/9/04, was appropriate due to fundamental differences between it and the leavepiece (ZY2394) at issue in Case AUTH/1634/9/04. The previous leavepiece was a mailing sent to psychiatrists and hospital pharmacists that included a table of data listing antipsychotics which were superior or equivalent to haloperidol.

The leavepiece now at issue was designed to allow a critical appraisal of Davis *et al*. The quotations cited

by Bristol-Myers Squibb and Otsuka were within the structured summary section of the folder. The structured summary clearly separated out the background, objectives, methods, main finding and conclusions. The summary was deliberately prepared in a non-promotional manner that was not designed to present anything other than the clear conclusions of Davis *et al*. Lilly considered that in contrast to the table in the previous leavepiece, the leavepiece now at issue, which included a full reprint of the published paper, avoided being too simplistic or misleading. Bristol-Myers Squibb and Otsuka had complained specifically about the following quotations from the paper:

- 'Other SGAs (e.g. quetiapine, aripiprazole) were not significantly different from FGAs'. This quote was taken verbatim from the results section in the abstract of the paper and thus the intention of the leavepiece was not to imply anything regarding the conclusions of the authors, but solely to state their conclusions. There was no statement regarding 'equivalence' in efficacy of aripiprazole and haloperidol in general, which was the focus of the ruling in Case AUTH/1634/9/04. Lilly noted that Bristol-Myers Squibb and Otsuka contended that the leavepiece did not attempt to place the findings of Davis *et al* in context by referring to the quotation 'Failure to find a statistically significant difference does not prove that these drugs are equal to FGAs because there is a possibility that further studies could demonstrate this'. The structured summary in the leavepiece at issue made no claims of 'equivalence', as per the previous ruling. The statement made 'Other SGAs (e.g. quetiapine, aripiprazole) were not significantly different from FGAs' was taken directly from the paper. Furthermore, the full paper was provided, and was intended to be part of this piece; therefore the full context was inherent in the way this material was designed.
- '… the rest of SGAs – e.g. quetiapine, aripiprazole (similar efficacy to that of FGAs)'. This second statement essentially repeated the first statement, as above and like the first statement, it was not a claim to equivalence. The arguments were identical. This was the wording that Davis *et al* used in the results section of the paper.

Lilly noted that Bristol-Myers Squibb and Otsuka alleged that the leavepiece now at issue stated unequivocally that the efficacy of aripiprazole was not significantly different to that of FGAs. The rulings in Case AUTH/1634/9/04 focussed on whether the table in the leavepiece previously at issue implied that Davis *et al* had unequivocally demonstrated equivalence, rather than 'no statistically significant difference in efficacy', which was the wording used by Davis *et al*. In contrast to this view Lilly contended that the item at issue thus accurately reflected the conclusions of Davis *et al* and thus there had been no breach of Clause 7.2. Lilly was also unaware of any relevant new data published since the Appeal Board hearing that might further address these issues.

Lilly submitted that it had taken all steps to avoid any breach of the Code similar to that ruled in Case AUTH/1634/9/04. The leavepiece now at issue was not covered by the undertakings given in relation to the previous case and did not breach the Code in its own right.

Furthermore, Lilly considered that the leavepiece at issue did not amount to 'similar material' to that used previously. The leavepiece now at issue contained a structured summary of Davis *et al* including verbatim quotations. It did not contain a table summarising all the evidence, which might, on the basis of the rulings in Case AUTH/1634/9/04, be regarded as either too simplistic or misleading. The leavepiece gave a fair and balanced impression of the study's conclusions. As such Lilly submitted there was no breach of Clauses 7.2, 9.1 or 22 and hence no breach of Clause 2.

PANEL RULING

The Panel considered that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in the future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted that the previous case, Case AUTH/1634/9/04 concerned, *inter alia*, a table of data which listed those antipsychotics which were significantly better than haloperidol and those antipsychotics which were equivalent to haloperidol (including, *inter alia*, aripiprazole). The Appeal Board upheld the Panel's ruling of breaches of the Code as it considered that the table of data was too simplistic; it implied that Davis *et al* had unequivocally demonstrated that haloperidol and aripiprazole were equivalent in terms of effectiveness, and that was not so.

Turning to the case now before it the Panel considered that the two page structured summary of Davis *et al* provided in the folder with the entire paper was sufficiently different in format and content to the material at issue previously (Case AUTH/1634/9/04) such that it was not caught by the undertaking given in that case. No breaches of Clauses 2, 9.1 and 22 were thus ruled.

The Panel noted Bristol-Myers Squibb's and Otsuka's allegation that the structured summary of Davis *et al* was in breach of the Code for reasons identical to those cited in Case AUTH/1634/9/04. In that regard the complainants referred to the statement that the efficacy of aripiprazole was not significantly different to that of the first generation antipsychotics (a group that included haloperidol). Case AUTH/1634/9/04 contained, *inter alia*, a general allegation that the material did not reflect the conclusion of Davis *et al*.

The Panel considered that its comments in the previous case about Davis *et al* were relevant to the present case. The Panel noted that Davis *et al* reviewed 142 controlled studies, however not all of the medicines were equally represented. For example 31 studies involving clozapine were included in the meta-analysis vs three for aripiprazole (n=560); (Carson *et al* 2001; Daniel *et al* 2000 and Petrie *et al* 1997). The data was thus more compelling that there was an advantage for clozapine vs haloperidol as opposed to the equivalence of haloperidol and

aripiprazole. Davis *et al* stated that 'Failure to find a statistically significant difference does not prove that these drugs are equal to [first generation antipsychotics] because there is a possibility that further studies could demonstrate this'.

The Panel noted that the structured summary at issue in the current case set out the background, objectives, methods and main findings of Davis *et al*. Some statements in the main findings section were emphasised by the use of upper case text. The first bullet point in this section described the effect sizes and p values of olanzapine, amisulpride, risperidone and olanzapine compared to FGAs as 'HIGHLY STATISTICALLY SIGNIFICANT – the best evidence of difference'. A subsequent bullet point began 'THREE EFFICACY GROUPS OF SGA have been established'. This was followed by 'Other SGAs (e.g. quetiapine, aripiprazole) were NOT significantly different from FGAs' beneath which the third bullet point read 'The rest of SGAs – e.g. quetiapine, aripiprazole (SIMILAR efficacy to that of FGAs)…'. There was no claim that aripiprazole had equivalent efficacy to haloperidol, the terms 'similar' and 'not statistically significant' had been used. The Panel considered, however, that the section implied that Davis *et al* had been unequivocal on this point and that was not so. The use of upper case text compounded the misleading impression given. A breach of Clause 7.2 was ruled.

Complaint received **30 August 2005**

Case completed **18 October 2005**

CASES AUTH/1757/9/05, AUTH/1759/9/05 and AUTH/1760/9/05

PRIMARY CARE TRUST HEAD OF PRESCRIBING, A GENERAL PRACTITIONER, A PRIMARY CARE TRUST DIRECTOR OF PUBLIC HEALTH AND A PRACTICE SUPPORT PHARMACIST v SERVIER

Coversyl booklet

The head of prescribing at a primary care trust (PCT), a general practitioner, the assistant director of public health together with a practice support pharmacist (both from the same PCT) all complained about a Coversyl (perindopril) booklet sent as part of a mailing by Servier to GPs, hospital doctors, primary care organisations and pharmacy advisors. The booklet, entitled 'The impact of the results of the ASCOT trial', summarised the study's design and results. ASCOT stood for Anglo-Scandinavian Cardiac Outcomes Trial and compared combinations of atenolol ± thiazide diuretic vs amlodipine ± perindopril.

The complainants were all concerned about the same section. Beneath the heading 'Clinical results:' was the following:

- **'BP was reduced by 27/17mmHg in both treatment arms**
- **Average BP at the end of the study was: 137/78mmHg**

The amlodipine ± COVERSYL treatment arm had superior benefits to the atenolol ± thiazide combination in reducing the risk of death, strokes and heart attacks. Results were consistent across all major predefined endpoints and sub-groups.'

In Case AUTH/1757/9/05 the head of prescribing at a PCT stated that in the first bullet point the figures were based upon a combined analysis of the entire trial cohort however the text implied that the blood pressures were similar in the two arms of the study. This was not so, blood pressures between the two arms of the study were significantly different at the end of the study, with the mean difference between the two arms over the trial being 2.7/1.9mmHg.

The second bullet point also applied to the entire trial population, again the two arms had differing blood pressures at the end of the study, the amlodipine arm being 136.1/77.4mmHg and the atenolol arm being 137.7/79.2mmHg (a difference of 1.6/1.8mmHg).

The complainant noted that the text beneath the two bullet points stated that the amlodipine arm was superior in preventing death, strokes and heart attacks. While this was supported by the trial for the first two conditions, there was nothing to support the final claim. It was also claimed that this superiority was consistent across all endpoints. Again, this was unsupported, the primary outcome was not significant and neither were two of the seven secondary endpoints, or three of the seven tertiary endpoints.

In Case AUTH/1759/9/05 the general practitioner similarly noted that the first bullet point suggested that the blood pressure lowering was the same in both arms of the study whereas the amlodipine arm saw an average reduction of 2.7/1.9mmHg compared to the atenolol based regime. This difference in blood pressure and not the medicine choice accounted for the difference observed in the two groups. The complainant noted that there were other possible confounders for the results observed. The real message was the lower the blood pressure the better.

The complainant considered that Servier must be aware of this fact and that the company had misrepresented the ASCOT data to promote perindopril as having some effect other than that of lower blood pressure.

In Case AUTH/1760/9/05 the assistant director of public health and the practice support pharmacist to a PCT noted the two bullet points and stated that the crucial word 'combined' as in 'both treatment arms combined', was missing. It clearly stated in the published paper that these figures were an average of both treatment arms combined. Immediately below these figures in the published paper it stated 'compared with those allocated the atenolol-based regimen, blood pressure values were lower throughout the trial in those allocated the amlodipine-based regimen. These differences were largest (5.9/2.4mmHg) at 3 months, and the average difference throughout the trial was 2.7/1.9mmHg'.

This information was not hard to miss and was crucial. The amlodipine-based regimen was better at lowering blood pressure than the atenolol-based regimen. This alone was likely to be the reason why there was a small reduction in secondary outcomes in the study, as expressed in the accompanying editorial. The wording in the booklet strongly suggested that there was no difference in blood pressure between the two treatment arms, which was obviously extremely misleading.

The complainants noted that these misleading figures were then followed by a statement that the amlodipine ± COVERSYL treatment arm had superior benefits to the atenolol ± thiazide combination, thereby creating the impression that this was due to some superiority inherent in the medicines used rather than the blood pressure difference that was produced. The key message from ASCOT (and other hypertension studies) was that what was important was the blood pressure lowering achieved rather than some other 'extra' property of the antihypertensive used.

In Cases AUTH/1757/9/05, AUTH/1759/9/05 and AUTH/1760/9/05 the Panel noted that the ASCOT trial was established to determine whether, for a given reduction in blood pressure, newer antihypertensives (amlodipine ± perindopril) conferred any advantages over older agents (ß-blockers ± diuretics). Treatment was titrated to achieve target blood pressure (<140/90mmHg for patients without diabetes and <130/80mmHg for those with diabetes). The results showed that, on average, in both treatment groups combined, blood pressure dropped from a mean 164/94.7mmHg to a mean 136.9/78.3mmHg ie an average reduction of 26.6/16.6mmHg. The Panel noted, however, that neither of the two bullet points at issue, 'BP was reduced by 27/17mmHg in both treatment arms' and 'Average BP at the end of the study was: 137/78mmHg' stated that the results cited were from the combined patient groups; it appeared that the figures quoted applied to each treatment group separately which was not so. Blood pressure at the final visit was lower in the amlodipine ± perindopril arm than in the atenolol ± diuretic arm (136.1/77.4mmHg vs 137.7/79.2mmHg respectively representing mean falls of 27.5/17.7mmHg and 25.7/15.6mmHg). The average difference in blood pressure between the two groups throughout the trial was 2.7/1.9mmHg. The Panel considered that the bullet points were misleading in their portrayal of the blood pressure data from the ASCOT trial. In the Panel's view readers should have been told that blood pressure was lower in the amlodipine ± perindopril group than the other group so that the outcome data could be put into the correct clinical context and the impact of the differences understood. A breach of the Code was ruled.

The Panel noted that the ASCOT trial had been stopped early because of the favourable results reported in the amlodipine ± perindopril arm. However, the early termination of the study meant that from a statistical standpoint the study was underpowered with respect to its primary endpoint (the risk of non-fatal myocardial infarction and fatal CHD) and so no statistically significant difference was shown in that regard between the two groups although there was a trend in favour of the amlodipine-based regimen. The authors also noted other possible explanatory factors for the results observed. With regard to the secondary endpoints, all cause mortality and fatal and non-fatal stroke, among others, showed statistically significant benefits for amlodipine ± perindopril vs atenolol ± diuretic.

The Panel noted the claim 'The amlodipine ± COVERSYL treatment had superior benefits to atenolol ± thiazide combination in reducing the risk of death, strokes and heart attacks. Results were consistent across all major predefined endpoints and sub-groups'. Although the claim with regard to reducing the risk of death and strokes could be substantiated from the secondary outcome data the ASCOT study had not included the endpoint 'heart attacks' and so this aspect of the claim could not be substantiated. The Panel further noted that, contrary to the claim, the results were not consistent across all major predefined endpoints and sub-groups. The primary outcome showed a non-significant statistical difference between the two treatment groups and there were also no statistically significant differences shown in one of the secondary endpoints (fatal and non-fatal heart failure) and in three of the tertiary endpoints (silent myocardial infarction, chronic stable angina and life threatening arrhythmias). The Panel considered that the claim was inaccurate and could not be substantiated. The Panel also considered that it was misleading not to inform readers that the death and stroke data related to secondary endpoints and that the primary endpoint had shown no statistically significant difference between the two treatment regimens. Breaches of the Code were ruled.

In Case AUTH/1759/9/05 the Panel further noted that the complainant had alleged that Servier had misrepresented the ASCOT data to promote perindopril as having some effect other than that of lower blood pressure. Servier had not addressed this point in its response.

The Panel noted that Coversyl was indicated for the treatment of hypertension and symptomatic heart failure. The Panel considered that the claims for a reduced risk of cardiovascular events with Coversyl treatment had been made within the context of treating hypertension. Whilst noting its ruling above with regard to the portrayal of the blood pressure data, the Panel nonetheless did not

consider that the mailing promoted Coversyl for anything other than the treatment of hypertension. No breach of the Code was ruled.

A head of prescribing at a primary care trust (PCT), a general practitioner and the assistant director of public health together with a practice support pharmacist (both from the same PCT) all complained about an eight-page Coversyl (perindopril) booklet (ref 06COASC117a) sent as part of a mailing by Servier Laboratories Ltd. The booklet, entitled 'The impact of the results of the ASCOT trial', summarised the study's design and results. ASCOT stood for Anglo-Scandinavian Cardiac Outcomes Trial and compared combinations of atenolol ± thiazide diuretic vs amlodipine ± perindopril. The mailing had been sent to GPs, hospital doctors, primary care organisations and pharmacy advisors.

The complainants were all concerned about the section on page four of the booklet which stated beneath the heading 'Clinical results:' the following:

- 'BP was reduced by 27/17mmHg in both treatment arms
- Average BP at the end of the study was: 137/78mmHg

  The amlodipine ± COVERSYL treatment arm had superior benefits to the atenolol ± thiazide combination in reducing the risk of death, strokes and heart attacks. Results were consistent across all major predefined endpoints and sub-groups.'

Case AUTH/1757/9/05

COMPLAINT

The head of prescribing at a PCT stated that in the first bullet point the figures were based upon a combined analysis of the entire trial cohort however the text implied that the blood pressures were similar in the two arms of the study. This was not the case, blood pressures between the two arms of the study were significantly different at the end of the study, with the mean difference between the two arms over the trial being 2.7/1.9mmHg.

The second bullet point also applied to the entire trial population, again the two arms had differing blood pressures at the end of the study, the amlodipine arm being 136.1/77.4mmHg and the atenolol arm being 137.7/79.2mmHg (a difference of 1.6/1.8mmHg).

The complainant noted that the text beneath the two bullet points stated that the amlodipine arm was superior in preventing death, strokes and heart attacks. While this was supported by the trial for the first two conditions, there was nothing to support the final claim. It was also claimed that this superiority was consistent across all endpoints. Again, this was unsupported, the primary outcome was not significant and neither were two of the seven secondary endpoints, or three of the seven tertiary endpoints.

Case AUTH/1759/9/05

COMPLAINT

The general practitioner noted that the first bullet point suggested that the blood pressure lowering was the same in both arms of the study whereas the amlodipine arm saw an average reduction of 2.7/1.9mmHg compared to the atenolol arm. This difference in blood pressure and not the medicine choice accounted for the difference observed in the two groups. The complainant noted that there were other possible confounders for the results observed. The real message was the lower the blood pressure the better.

The complainant considered that Servier must be aware of this fact and he considered that the company had misrepresented the ASCOT data to promote perindopril as having some effect other than that of lower blood pressure.

Case AUTH/1760/9/05

COMPLAINT

The assistant director of public health and the practice support pharmacist to a PCT noted that the crucial word 'combined' as in 'both treatment arms combined', was unfortunately missing from the two bullet points. It clearly stated in the published paper, in the section from which these figures had been drawn, that they were an average of both treatment arms combined. Immediately below these figures in the published paper it stated 'compared with those allocated the atenolol-based regimen, blood pressure values were lower throughout the trial in those allocated the amlodipine-based regimen. These differences were largest (5.9/2.4mmHg) at 3 months, and the average difference throughout the trial was 2.7/1.9mmHg'.

This information was not hard to miss and was crucial. The amlodipine-based regimen was better at lowering blood pressure than the atenolol-based regimen. This alone was likely to be the reason why there was a small reduction in secondary outcomes in the study, as expressed in the accompanying editorial. The wording in the booklet strongly suggested that there was no difference in blood pressure between the two treatment arms, which was obviously extremely misleading.

The complainants noted that these misleading figures were then followed by a statement that the amlodipine ± COVERSYL treatment arm had superior benefits to the atenolol ± thiazide combination, thereby creating the impression that this was due to some superiority inherent in the medicines used rather than the blood pressure difference that was produced. The key message from ASCOT (and other hypertension studies) was that what was important was the blood pressure lowering achieved rather than some other 'extra' property of the antihypertensive used.

* * * * *

In all 3 cases the Authority asked Servier to respond in relation to Clauses 7.2 and 7.4. In Case AUTH/1759/9/05 Servier was also asked to respond in relation to Clause 3.2.

RESPONSE

Servier submitted an identical response to all three complaints.

Servier explained that the benefits of antihypertensive therapy for the prevention of cardiovascular mortality and morbidity were well established, however, no individual trial had shown a significant reduction in coronary heart disease (CHD) events. Data on the relative effects of newer antihypertensives compared with standard treatment options, especially in combination treatment regimens was very limited.

Which antihypertensives should be used first-line had been the subject of debate and controversy for many years. To reach blood pressure targets recommended in national and international guidelines, most patients would need two or more antihypertensives. In fact, European and American guidelines recommended that patients should be able to be initiated on combination therapy despite the lack of clinical trial evidence for the optimum combinations of antihypertensives. As a result of this absence of trial evidence, guidelines often recommended different combinations of antihypertensives. The ASCOT study was set up to determine which combination was better, 'old' or 'new'.

When the ASCOT trial was initiated the most frequent antihypertensive combination used worldwide was a ß-blocker (atenolol) plus a diuretic (bendroflumethiazide). Therefore these two medicines were the logical choice as the reference comparators. It was widely accepted that ß-blockers and diuretics had not demonstrated beneficial effects on coronary events (often ascribed to their adverse metabolic effects). As far as selecting the test combination was concerned, there was an obvious need for further efficacy and safety data for calcium channel blockers and ACE inhibitors. Consequently, along with the favourable metabolic profiles of calcium channel blockers and ACE inhibitors the ASCOT investigators chose to compare the effect on non-fatal myocardial infarction and fatal CHD of a combination of the calcium channel blocker amlodipine and the ACE inhibitor perindopril with that of a ß-blocker and diuretic.

More than 19,000 patients were included in this multicentre, prospective, randomised controlled trial in hypertensive patients, aged 40-79 and with at least three other cardiovascular risk factors. Patients were treated with either the 'newer agents', amlodopine 5-10mg adding perindopril 4-8mg as required (n = 9639) or 'the older agents', atenolol 50-100mg adding bendroflumethiazide 1.25-2.5mg as required (n = 9618). The primary endpoint was the combined endpoint of non-fatal MI (including silent) + fatal CHD. Secondary endpoints were: total CV events and procedures; total coronary endpoint; non-fatal MI (excluding silent) + fatal CHD; all-cause mortality; CV mortality; fatal + non-fatal stroke and fatal and non-fatal heart failure. Tertiary endpoints included: silent myocardial infarction; unstable angina; chronic stable angina; peripheral arterial disease; life-threatening arrhythmias; development of diabetes mellitus and development of renal impairment.

Servier noted that the ASCOT study was powered such that approximately 18,000 patients needed to be followed up for an average of five years or in the study overall a total of 1150 patients had a primary endpoint. As far as blood pressure lowering was concerned the antihypertensive therapy was titrated to achieve target blood pressures in both groups (<140/90mmHg for patients without diabetes and <130/80mmHg for diabetics). The ASCOT study was set up to see whether there was a difference in serious cardiovascular endpoints between two antihypertensive treatments ie the traditional regimen of ß-blocker and diuretic with the newer regimen of calcium channel blocker and ACE inhibitor. Servier noted that the ASCOT study was not designed to show a blood pressure lowering advantage in either of the two treatment regimens.

Servier stated that in November 2005, ie more than a year early, the Data and Safety Monitoring Board (DSMB) was obliged to stop the ASCOT trial due to the reduction of all-cause and cardiovascular mortality in the amlodopine ± perindopril arm compared to the atenolol ± bendroflumethiazide arm. 19,257 patients were followed up with an accumulated total of 106,153 patients years of observation. However, there had only been 903 primary endpoints in the study overall due to early termination of the study (the study was powered for at least 1150 individuals to experience the primary endpoint).

The primary endpoint of non-fatal MI (including silent) + fatal CHD was reduced by 10% in the amlodopine ± perindopril group. Whilst this was not statistically significant it was largely in favour of amlodopine ± perindopril. The post hoc endpoint of cardiovascular death + myocardial infarction + stroke further supported this trend showing a statistically significant reduction in favour of amlodopine ± perindopril of 16% (p= 0.003). The ASCOT investigators stated that the primary endpoint did not show statistical significance because of the early termination of the study (the study was powered for 1150 individuals to have such events whereas only 903 had arisen at last follow-up).

All secondary endpoints were in favour of amlodopine ± perindopril. Two were not statistically significant (non-fatal myocardial infarction (excluding silent) + fatal CHD and fatal and non-fatal heart failure) but as they were in favour of amlodopine ± perindopril they were consistent with the other results ie no secondary endpoint favoured atenolol ± bendroflumethiazide. Servier emphasised that the number of events that occurred was much lower than the study was powered for due to early termination of the study. It was highly likely that if the study continued that these two endpoints would have reached statistical significance.

Similarly all but three of the tertiary endpoints (silent myocardial infarction, chronic stable angina and life-threatening arrhythmias) were statistically significant in favour of amlodopine ± perindopril. Therefore, tertiary endpoint results were consistent with all other endpoint (primary, secondary and post-hoc) results. For the three endpoints that did not achieve statistical significance the number of events added together were only approximately 5% of the total number of events in the entire study. Again, Servier emphasised

that the number of events that occurred was much lower than the study was powered for due to its early termination.

Servier stated that the impact and importance of the ASCOT study results could not be over stated. The investigators had stated 'ASCOT is a belter of a trial and well done to the investigators. The results are powerful and persuasive, and prescribing in hypertension will surely follow' and 'ASCOT was really a comparison of regimens, since most patients in each group were taking combination therapy. Yet the results were little short of stunning'. Further, the discussion of the publication of the ASCOT study in the Lancet began: 'The findings of ASCOT-BLA [blood pressure lowering arm] show that in hypertensive patients at moderate risk of developing cardiovascular events, an antihypertensive drug regimen starting with amlodopine adding perindopril as required is better than one starting with atenolol adding thiazide as required in terms of reducing the incidence of all types of cardiovascular events and all-cause mortality, and in terms of risk of new-onset diabetes'.

One of the investigators had stated: 'These results are hugely significant for the future management of hypertension. The health benefits associated with amlodopine/perindopril compared with atenolol/bendroflumethiazide raise concerns about the future place of ß-blockers as first-line treatment choice for hypertension. What we expect, at least in the UK, is a meeting of the guideline committee to re-evaluate the future place of beta blockers as first-line treatment in hypertension'. It had also been stated that '… blood pressure control was better early on with the amlodopine/perindopril combination, but levels were virtually identical by the end of the trial. The mean difference was 2.9/1.8mmHg throughout the course of the study, which Dr Dahlöf said was insufficient to explain the mortality difference'.

In the commentary to the above it was stated that '… importantly, most of the endpoints were later in the trial, when blood pressures were evenly matched'.

This was confirmed by the ASCOT study investigators who stated '…a 2.7mmHg systolic blood-pressure difference (the average difference between the two groups throughout ASCOT-BPLA) would be expected to generate a difference of only 4-8% in coronary events and 11-14% in strokes…'. Servier noted, however, that there was a 16% decrease in coronary events and a 23% decrease in stroke, and considered therefore that the small difference in blood pressure between the two treatment groups did not explain the difference in cardiovascular events.

In summary, ASCOT was a landmark study which would have a significant impact on the treatment of hypertension and it was in this context that the mailing at issue was developed. The results categorically demonstrated that treating hypertensive patients with amlodopine ± perindopril saved significantly more lives compared to treating patients with atenolol ± bendroflumethiazide. These results were of such significance that the National Institute for health and Clinical Excellence and the British Hypertension Society announced within days of the data release that they would review jointly the hypertension guidelines in light of the results.

The mailing was intended to provide a clear and concise outline of the ASCOT study design, entry criteria, targets and endpoints as was clear from its title 'The impact of the results of the ASCOT trial' 'Study summary'. Page 4 of mailing included the heading 'Clinical results' with two bullet points: 'BP was reduced by 27/17mmHg in both treatment arms and 'Average BP at the end of the study was: 137/78mmHg'. These bullet points clearly demonstrated to the reader that blood pressure targets (ie <140/90mmHg as described on page 3) had been achieved in both treatment groups.

The ASCOT study was not designed to demonstrate superiority of one treatment regimen over another in terms of blood pressure lowering. Both treatment regimens were titrated to meet blood pressure target ie <140/90mmHg. The two bullet points simply informed the reader that blood pressures were lowered by similar amounts in both groups and met the pre-defined target set in the study protocol. As stated above, leading cardiologists described blood pressures in the two treatment groups in the ASCOT trial as 'virtually identical' and 'evenly matched' (ASCOT investigators (2005).

Also, as stated above, although there was a small, difference in blood pressures between the two treatment groups this could not account for the differences in endpoint reductions and Servier did not consider that the way this data had been presented was misleading or incapable of substantiation. If the bullet points had been presented differently informing readers of the small differences in blood pressure the results and messages conveyed by the mailing would still be the same. For example the ASCOT study investigators in the study publication stated that the average blood pressure difference between the two groups would be expected to generate a difference of only 4-8% in coronary events and 11-14% in stroke. There was, however, a 16% decrease in coronary events and a 23% decrease in stroke, therefore the small difference in blood pressure between the two treatment groups did not explain the difference in cardiovascular events.

In summary the ASCOT study was designed to compare two antihypertensive treatment regimens in terms of serious cardiovascular endpoints; it was not set up to demonstrate any superiority in blood pressure lowering between the two treatment groups. The small difference in blood pressure between the two treatment groups did not explain the large difference in cardiovascular outcomes between the two groups. Even if the small differences in blood pressure between the two groups was mentioned in the mailing it would not change any of the messages or interpretation of the messages in this mailing.

Servier considered that the mailing did what it was designed to do, ie it provided health professionals with a 'Study summary' which clearly conveyed 'The impact of the results of the ASCOT trial'. Servier therefore submitted that the mailing was not in breach of the Code.

PANEL RULING

Cases AUTH/1757/9/05, AUTH/1759/9/05 and AUTH/1760/9/05

The Panel noted that the ASCOT trial was established to determine whether, for a given reduction in blood pressure, newer antihypertensives (amlodipine ± perindopril) conferred any advantages over older agents (ß-blockers ± diuretics). Patients in both arms of the study had their treatment titrated to achieve target blood pressure (<140/90mmHg for patients without diabetes and <130/80mmHg for those with diabetes). The published results showed that, on average, in both treatment groups **combined**, blood pressure dropped from a mean 164/94.7mmHg to a mean 136.9/78.3mmHg ie an average reduction of 26.6/16.6mmHg. The Panel noted, however, that neither of the two bullet points at issue, 'BP was reduced by 27/17mmHg in both treatment arms' and 'Average BP at the end of the study was: 137/78mmHg' stated that the results cited were from the **combined** patient groups; it appeared that the figures quoted applied to each treatment group separately which was not so. Blood pressure at the final visit was lower in the amlodipine ± perindopril arm than in the atenolol ± diuretic arm (136.1/77.4mmHg vs 137.7/79.2mmHg respectively representing mean falls of 27.5/17.7mmHg and 25.7/15.6mmHg). The average difference in blood pressure between the two groups throughout the trial was 2.7/1.9mmHg. The Panel considered that the bullet points were misleading in their portrayal of the blood pressure data from the ASCOT trial. In the Panel's view readers should have been told that blood pressure was lower in the amlodipine ± perindopril group than the other group so that the outcome data could be put into the correct clinical context and the impact of the differences understood. A breach of Clause 7.2 was ruled.

The Panel noted that the ASCOT trial had been stopped early because of the favourable results reported in the amlodipine ± perindopril arm. However, the early termination of the study meant that from a statistical standpoint the study was underpowered with respect to its primary endpoint (the risk of non-fatal myocardial infarction and fatal CHD) and so no statistically significant difference was shown in that regard between the two groups although there was a trend in favour of the amlodipine-based regimen. The authors also noted other possible explanatory factors for the results observed. With regard to the secondary endpoints, all cause mortality and fatal and non-fatal stroke, among others, showed statistically significant benefits for amlodipine ± perindopril vs atenolol ± diuretic.

The Panel noted the claim 'The amlodipine ± COVERSYL treatment had superior benefits to atenolol ± thiazide combination in reducing the risk of death, strokes and heart attacks. Results were consistent across all major predefined endpoints and sub-groups'. Although the claim with regard to reducing the risk of death and strokes could be substantiated from the secondary outcome data the ASCOT study had not included the endpoint 'heart attacks' and so this aspect of the claim could not be substantiated. The Panel further noted that, contrary to the claim, the results were not consistent across all major predefined endpoints and sub-groups. The primary outcome showed a non-significant statistical difference between the two treatment groups and there were also no statistically significant differences shown in one of the secondary endpoints (fatal and non-fatal heart failure) and in three of the tertiary endpoints (silent myocardial infarction, chronic stable angina and life threatening arrhythmias). The Panel considered that the claim was inaccurate and could not be substantiated. The Panel also considered that it was misleading not to inform readers that the death and stroke data related to secondary endpoints and that the primary endpoint had shown no statistically significant difference between the two treatment regimens. Breaches of Clauses 7.2 and 7.4 were ruled.

Case AUTH/1759/9/05

The Panel noted that the complainant had alleged that Servier had misrepresented the ASCOT data to promote perindopril as having some effect other than that of lower blood pressure. Servier had not addressed this point in its response.

The Panel noted that Coversyl was indicated for the treatment of hypertension and symptomatic heart failure. The Panel noted Servier's submission that the benefits of antihypertensive therapy for the prevention of cardiovascular mortality and morbidity were well established. There was, however, a difference between promoting a product for a licensed indication and promoting the benefits of treating a condition. Whilst it was not necessarily unacceptable to refer to such benefits in promotional material such references should comply with the Code and should only be made within the context of treating patients for the product's licenced indications.

The Panel considered that the claims for a reduced risk of cardiovascular events with Coversyl treatment had been made within the context of treating hypertension. Whilst noting its ruling of a breach of Clause 7.2 above with regard to the portrayal of the blood pressure data, the Panel nonetheless did not consider that the mailing promoted Coversyl for anything other than the treatment of hypertension. No breach of Clause 3.2 was ruled.

Complaints received:

AUTH/1757/9/05	**12 September 2005**
AUTH/1759/9/05	**20 September 2005**
AUTH/1760/9/05	**21 September 2005**
Cases completed	**8 November 2005**

CASE AUTH/1762/10/05

PRIMARY CARE TRUST CLINICAL EFFECTIVENESS PHARMACIST v MERCK SHARP & DOHME

Promotion of Cozaar

A clinical effectiveness pharmacist at a primary care trust complained that materials issued by Merck Sharp & Dohme misrepresented the British Hypertension Society's (BHS) recommendations for combining antihypertensives. The items at issue, an A4 card, an A3 poster and a mouse mat, featured a treatment 'flow chart' which appeared to be identical to that published by the BHS in its guidelines for the management of hypertension. A box of text in the published guidelines explained that 'A' in the AB/CD algorithm stood for 'ACE Inhibitor or angiotensin receptor blocker [AIIA]'. In the guidelines distributed by Merck Sharp & Dohme the order of the two classes of medicines had been reversed such that it was stated that 'A' represented 'Angiotensin II Antagonist or ACE Inhibitor'. The complaint alleged that the material thus highlighted AIIAs in preference to ACE inhibitors and distorted the BHS guidelines to such an extent that they no longer reflected those originally published.

With regard to the A4 card the complainant noted that it had a prominent BHS logo in the body of the material and a small Merck Sharp & Dohme logo at the bottom. Many GPs had this poster on their surgery wall but might miss the subtle, but important change of the word ordering.

The Panel noted that the presentation of the BHS recommendations on the poster mimicked the style of the original published AB/CD algorithm. The text explaining what 'A' stood for had, however, been changed such that the order of 'ACE inhibitor or angiotensin receptor blocker' had been reversed.

The Panel noted that the published guidelines contained a section headed 'Recommendations for drug selection in practice – The BHS AB/CD algorithm' which explained that the AB/CD protocol was not restrictive and provided a template that allowed the use of all classes of antihypertensive medicine. All things being equal and when there was no compelling indication for treatment with a specific class of medicine, then the cheapest should be used. This explanation was not included in the guidelines distributed by Merck Sharp & Dohme.

The Panel considered that the layout of the A4 card was such that readers would assume they were reading the BHS guidelines as published and this was not so. Given that AIIAs were mentioned before ACE inhibitors readers might assume that AIIAs were the first choice of medicine to be used for blocking the rennin-angiotensin system. The Panel noted that the additional information that where a choice existed then the cheapest medicine should be chosen was not included on the A4 card. The Panel considered that, on balance, the card was misleading as alleged. A breach of the Code was ruled.

The A3 poster, in addition to showing the company's version of the BHS recommendations for treating blood pressure featured the Cozaar product logo and the following claims: 'Where should COZAAR be considered? In line with the BHS ABCD algorithm, COZAAR could be used rather than a beta-blocker, when calcium channel-blockers or diuretics provide inadequate control' and 'What the BHS say about the LIFE trial with COZAAR? "… the LIFE trial raises the possibility of stroke protection with AIIA-based treatments that add to the benefit of BP lowering"'.

The complainant noted that the poster was essentially the same as the A4 card, except specific claims were made about Cozaar and a large product logo was featured and parts of the original BHS guidance were quoted. The complainant alleged that the selective quotations were misleading and for very specific patient groups, not the wider hypertensive patients, of whom only around 15% were truly ACE intolerant. Guidance from the National Institute for Health and Clinical Excellence (NICE) stated that AIIAs should only be used where ACE inhibitors were not tolerated.

The effects quoted might just be an indication of BP lowering, rather than the influence of any specific medicine.

The Panel considered that its comments regarding the layout and the content of the A4 card considered above, were relevant. In addition to the modified AB/CD algorithm the poster featured the Cozaar logo which emphasised the medicine class AIIA. The Panel considered the addition of the Cozaar logo, together with the reversal of the 'A' medicines, strengthened the impression that the BHS recommended AIIAs before ACE inhibitors. Again the BHS advice that, all things being equal, the least expensive medicine should be used, was not included on the poster. The Panel considered that the poster was misleading as alleged. A breach of the Code was ruled.

The Panel noted that the poster included the claim that, in line with the BHS algorithm, 'Cozaar could be used rather than a beta-blocker, when calcium-channel blockers or diuretics provide inadequate control'. The Panel considered that the claim implied that the BHS specifically recommended Cozaar for some patients which was not so. The Panel further noted that, according to the BHS guidelines, when a calcium channel blocker or diuretic proved inadequate then an ACE inhibitor or AIIA could be used in preference to a beta-blocker. The prescriber thus had the choice of two medicine classes and not just one as implied by the claim. The Panel considered that the claim was misleading. A breach of the Code was ruled.

The Panel noted that the poster featured the quotation from the BHS guidelines '… the LIFE trial raises the possibility of stroke protection with AIIA-based treatments that add to the benefit of BP lowering'. This sentence in the published paper

was followed by 'However, controversy remains as to whether this reflects less effective stroke prevention afforded by beta-blockade, as suggested by some earlier trial evidence'. The Panel considered that without this qualification the claim on the poster was misleading as alleged. A breach of the Code was ruled.

The complainant alleged that the mouse mat had distorted both the spirit and the substance of the BHS guidance. It too had re-ordered AIIA before ACE inhibitor, but had quite deliberately highlighted the 'A' throughout the algorithm. The distortion was compounded by highlighting AIIA in the key in bold capitals. The complainant alleged that the mouse mat attempted to lead GPs inappropriately and could be misconstrued by patients. A hypertensive patient seeing the mat on a GP's desk, might ask why they were not being prescribed this medicine or class of medicines as it was obviously more important/effective etc since it was given greatest prominence.

The Panel considered that its comments regarding the layout and content of the A4 card and the A3 poster above were relevant. In addition the emboldening of the 'A' throughout the algorithm and the use of upper case bold for Angiotensin II antagonist, as opposed to lower case bold for ACE inhibitor further emphasised the medicine class AIIA. Again the BHS advice that, all things being equal, the least expensive medicine should be used, was not included. The Panel considered that the mouse mat was misleading as alleged. A breach of the Code was ruled.

A clinical effectiveness pharmacist at a primary care trust (PCT), complained about materials issued by Merck Sharp & Dohme Limited which depicted the British Hypertension Society's (BHS) recommendations for combining antihypertensives. The items at issue were an A4 card (ref 04-05 CZR.04.10114.P.3Om.H0.0205 R), an A3 poster (ref 03-06 CZR.05.GB.10354.P) and a mouse mat (ref 10-05 CZR.04.GB.10244.0). The A3 poster and the mouse mat, in addition to depicting the BHS recommendations, also promoted Cozaar (losartan), an angiotensin II antagonist (AIIA) for the treatment of hypertension.

All of the materials featured a treatment 'flow chart' which appeared to be identical to that published by the BHS in its guidelines for the management of hypertension (Williams *et al* 2004). A box of text in the published guidelines explained that 'A' in the AB/CD algorithm stood for 'ACE Inhibitor or angiotensin receptor blocker [AIIA]'. In the guidelines distributed by Merck Sharp & Dohme the order of the two classes of medicines had been reversed such that it was stated that 'A' represented 'Angiotensin II Antagonist or ACE Inhibitor'.

The complainant alleged that the materials were very misleading and that they needed to be withdrawn and a correction published. He had contacted the company but was unhappy with its response.

The complainant understood that the BHS had asked its 'friends' to distribute copies of the ABCD algorithm to GPs and other health professionals. The BHS organised the printing for which the companies (including Merck Sharp & Dohme) paid, then distributed via their representatives. The complainant was concerned that Merck Sharp & Dohme had subtly but deliberately amended the published guidance to highlight the prominence of AIIAs so as to produce a commercial benefit for Cozaar.

The complaint alleged that the material at issue, distributed via post and at a conference, misrepresented the published BHS guidance by highlighting AIIAs in preference to ACE inhibitors. The level of distortion increased in the order of the A4 card, A3 poster and was greatest in the mouse mat. The complainant considered that the BHS guidelines had been distorted by Merck Sharp & Dohme to such an extent that they no longer reflected the original published paper.

The links between the BHS and its 'friends' – all pharmaceutical companies, 75% of which produced AIIAs – were so close that it appeared that financial conflicts of interest had been put ahead of patients' best interests.

When writing to Merck Sharp & Dohme, the Authority asked it to consider the requirements of Clause 7.2 of the Code.

1 A4 card

COMPLAINT

The complainant noted that this card had a prominent BHS logo in the body of the material and a small Merck Sharp & Dohme logo at the bottom. Merck Sharp & Dohme had claimed that the BHS approved this adapted version. Many GPs had this poster on their surgery wall. A health professional might miss the subtle, but important change of the word ordering.

RESPONSE

Merck Sharp & Dohme stated that this was a non-promotional item. The company explained that the BHS approached all 'friends' – including pharmaceutical companies and other interested parties – to help distribute its guidelines, produced in March 2004, in order to increase awareness amongst prescribers. Merck Sharp & Dohme offered to support the printing costs for 20,000 copies, which it would distribute via its sales force. The BHS allowed Merck Sharp & Dohme to reverse the order of AIIAs and ACE inhibitors in the AB/CD algorithm. In line with the Code, the copies of the guidelines distributed by Merck Sharp & Dohme carried a clear sponsorship statement.

Merck Sharp & Dohme did not consider that the fact that angiotensin II antagonists featured before ACE inhibitors under the 'A' medicine heading meant that the version of the guidelines it had distributed was misleading. The BHS considered both classes of medicine to be equivalent in terms of efficacy and evidence, unless there were compelling indications, where one class was considered superior to the other. These compelling indications for angiotensin II antagonists and ACE inhibitors were included in the full BHS guidelines. Merck Sharp & Dohme

understood that this was the reason the BHS agreed to its request to reverse the order of the two classes of medicine. Merck Sharp & Dohme believed that the BHS was satisfied with its approval and distribution of these guidelines. The company denied a breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that the presentation of the BHS recommendations on the poster mimicked the style of the original AB/CD algorithm published by the BHS (Williams *et al*). The text explaining what 'A' stood for had, however, been changed such that the order of 'ACE inhibitor or angiotensin receptor blocker' had been reversed. The guidelines distributed by Merck Sharp & Dohme stated that 'A' stood for 'Angiotensin II Antagonist or ACE Inhibitor'.

The Panel noted that the published guidelines contained a section headed 'Recommendations for drug selection in practice – The BHS AB/CD algorithm' which explained that the AB/CD protocol was not restrictive and provided a template that allowed the use of all classes of antihypertensive medicine. All things being equal and when there was no compelling indication for treatment with a specific class of medicine, then the cheapest should be used. This explanation was not included in the guidelines distributed by Merck Sharp & Dohme.

The Panel considered that the layout of the A4 card was such that readers would assume they were reading the BHS guidelines as published and this was not so. Given that AIIAs were mentioned before ACE inhibitors readers might assume that AIIAs were the first choice of medicine to be used for blocking the rennin-angiotensin system. The Panel noted that the additional information that where a choice existed then the cheapest medicine should be chosen was not included on the A4 card. The Panel considered that, on balance, the card was misleading as alleged. A breach of Clause 7.2 was ruled.

2 A3 poster

The A3 poster, in addition to showing the company's version of the BHS recommendations for treating blood pressure featured the Cozaar product logo in the bottom right hand corner. The following claims appeared along the bottom edge: 'Where should COZAAR be considered? In line with the BHS ABCD algorithm, COZAAR could be used rather than a beta-blocker, when calcium channel-blockers or diuretics provide inadequate control' and 'What the BHS say about the LIFE trial with COZAAR? "… the LIFE trial raises the possibility of stroke protection with AIIA-based treatments that add to the benefit of BP lowering"'. Both claims were referenced to Williams *et al*.

COMPLAINT

The complainant noted that the poster was essentially the same as the A4 card, except specific claims were made about Cozaar and a large product logo was featured and parts of the original BHS guidance were quoted.

The complainant alleged that the selective quotations were misleading and for very specific patient groups, not the wider hypertensive patients, of whom only around 15% were truly ACE intolerant. Guidance from the National Institute for Health and Clinical Excellence (NICE) stated that AIIAs should only be used where ACE inhibitors were not tolerated.

The effects quoted might just be an indication of BP lowering, rather than the influence of any specific medicine.

RESPONSE

Merck Sharp & Dohme stated that the A3 poster was designed as a promotional leavepiece. The brand name Cozaar was clearly marked on it, and the prescribing information was attached. The selected quotations were taken directly from the BHS guidelines, which used the LIFE trial as the main reference in describing the benefit associated with AIIA-based therapy in stroke prevention in hypertensive patients. Merck Sharp & Dohme considered that this was consistent with the BHS recommendations for treatment of uncontrolled hypertensive patients over the age of 55 years, requiring an 'A' drug. The suggestion that Cozaar could be considered rather than a beta-blocker, when a calcium channel-blocker or diuretic provided inadequate control, was in line with the recommendations.

PANEL RULING

The Panel considered that its comments regarding the layout and the content of the A4 card considered at point 1 above, were relevant. In addition to the modified AB/CD algorithm the poster featured the Cozaar logo which emphasised the medicine class AIIA. The Panel considered the addition of the Cozaar logo, together with the reversal of the 'A' medicines, strengthened the impression that the BHS recommended AIIAs before ACE inhibitors. Again the BHS advice that, all things being equal, the least expensive medicine should be used, was not included on the poster. The Panel considered that the poster was misleading as alleged. A breach of Clause 7.2 was ruled.

The Panel noted that the poster included the claim that, in line with the BHS algorithm, 'Cozaar could be used rather than a beta-blocker, when calcium-channel blockers or diuretics provide inadequate control'. The Panel considered that the claim implied that the BHS specifically recommended Cozaar for some patients which was not so. The Panel further noted that, according to the BHS guidelines, when a calcium channel blocker or diuretic proved inadequate then an ACE inhibitor or AIIA could be used in preference to a beta-blocker. The prescriber thus had the choice of two medicine classes and not just one as implied by the claim. The Panel considered that the claim was misleading. A breach of Clause 7.2 was ruled.

The Panel noted that the poster featured the quotation from the BHS guidelines '… the LIFE trial raises the possibility of stroke protection with AIIA-based

treatments that add to the benefit of BP lowering'. This sentence in the published paper was followed by 'However, controversy remains as to whether this reflects less effective stroke prevention afforded by beta-blockade, as suggested by some earlier trial evidence'. The Panel considered that without this qualification the claim on the poster was misleading as alleged. A breach of Clause 7.2 was ruled.

3 Mouse mat

COMPLAINT

The complainant alleged that this item distorted both the spirit and the substance of the BHS guidance. It too had re-ordered AIIA before ACE inhibitor, but had quite deliberately highlighted the 'A' throughout the algorithm. The distortion was compounded by highlighting AIIA in the key in bold capitals. The complainant alleged that the mouse mat attempted to lead GPs inappropriately and could be misconstrued by patients. A hypertensive patient visiting their GP and seeing the mat on the GP's desk, might ask why it was that they were not being prescribed this medicine or class of medicines over any other as it was obviously more important/effective etc since it was the class which was highlighted in capitals and given greatest prominence. The A1 treatment was the one highlighted, why are you not giving this to me?

RESPONSE

Merck Sharp & Dohme stated that the mouse mat was similar to the poster and was also clearly promotional. The fact that the 'A' medicine was highlighted was to indicate where Cozaar, which was quite clearly being advertised, fitted into the general picture of the AB/CD algorithm. Once again, the Cozaar logo and prescribing information were in evidence. Merck Sharp & Dohme denied a breach of Clause 7.2.

PANEL RULING

The Panel considered that its comments regarding the layout and content of the A4 card (point 1 above) and the A3 poster (point 2 above) were relevant. In addition the emboldening of the 'A' throughout the algorithm and the use of upper case bold for Angiotensin II antagonist, as opposed to lower case bold for ACE inhibitor further emphasised the medicine class AIIA. Again the BHS advice that, all things being equal, the least expensive medicine should be used, was not included. The Panel considered that the mouse mat was misleading as alleged. A breach of Clause 7.2 was ruled.

Complaint received **3 October 2005**

Case completed **6 December 2005**

CASE AUTH/1763/10/05

PRIMARY CARE TRUST CLINICAL EFFECTIVENESS PHARMACIST v SERVIER

Coversyl mailing

A clinical effectiveness pharmacist to a primary care trust (PCT), alleged that a mailing (an outer wallet and an 8 page booklet) for Coversyl (perindopril) issued by Servier was very misleading. The wallet bore the statement 'News just in: The ASCOT results are OUT!'. The booklet, entitled 'The impact of the results of the ASCOT trial', summarised the study's design and results. ASCOT stood for Anglo Scandinavian Cardiac Outcomes Trial which compared combinations of atenolol ± thiazide diuretic vs amlodipine ± perindopril. The materials featured the Coversyl logo and the strapline 'Control hypertension. Reduce risk' throughout.

The complainant noted that the booklet was dated August 2005 and used data on file. By definition this could not quote ASCOT data as the trial was not published until September. This could therefore misrepresent the published trial data.

The Panel noted that the mailing had been prepared in August 2005, the month before the ASCOT results had been published. The data in the material was referenced to data on file. In the Panel's view it would not be unusual for study sponsors to be aware of results before they were published and to prepare material to coincide with publication. Use of data in this way was not misleading *per se*. The Panel ruled no breach of the Code.

With regard to the claim 'There was also a trend towards a reduction in the combination of total CHD and non-fatal MI (the primary endpoint) in favour of amlodipine ± COVERSYL over atenolol ± bendroflumethiazide (4.5% vs. 4.9% p=0.11)' the complainant stated that by definition there could be no 'trend' in statistics, a result was either significant or it was not. At p=0.11, it was not close to the arbitrary p=0.05 usually used to define statistical significance, so this was an invalid claim.

The complainant noted that a chart in the booklet relating to secondary outcomes was different to that in the published paper. The confidence intervals were not stated in the booklet, however the 'non-fatal MI (excl silent) and fatal CHD' appeared to cross the line of significance, whereas in the published paper the harm rate was quoted as 0.87 with a 95% CI of 0.76-1.00. The complainant questioned the data source for this assertion as the two were at least not consistent and at worst incorrect.

The Panel noted that ASCOT had not shown a statistically significant difference between amlodipine ± perindopril vs atenolol ± bendroflumethiazide with regard to decreased risk of total CHD and non-fatal MI. The Panel did not consider the claim that there was a trend in favour of amlodipine ± perindopril negated the impression that there was a statistically proven advantage for that regimen; the claim was misleading in that regard. The Panel further considered that the misleading impression of the claim was strengthened by the claim 'Coversyl has something to celebrate: the ASCOT results' which appeared at the top of the page and the strapline 'Control hypertension. Reduce risk' which appeared at the bottom. A breach of the Code was ruled.

With regard to the chart in the booklet, the Panel noted that Servier had acknowledged that, due to a technical error, the results in the published paper had not been accurately reproduced. A breach of the Code was ruled.

With regard to the following two claims 'BP was reduced by 27/17mmHg in both treatment arms' and 'Average BP at the end of the study was: 137/78mmHg' the complainant noted that the crucial word 'combined' was missing. It should have stated in 'both treatment arms combined', as stated in the published paper.

Immediately below these figures in the published paper it stated 'compared with those allocated the atenolol-based regimen, blood pressure values were lower throughout the trial in those allocated the amlodipine-based regimen. These differences were largest (5.9/2.4mmHg) at 3 months, and the average difference throughout the trial was 2.7/1.9mmHg'. This crucial information was not hard to miss. The amlodipine-based regimen lowered blood pressure better than the atenolol-based regimen. This alone was likely to be the reason why there was a small reduction in secondary outcomes in the study, as expressed in the accompanying editorial. The wording in the booklet strongly suggested that there was no difference in blood pressure between the two treatment arms, which was obviously extremely misleading.

These misleading figures were then followed by a statement that the amlodipine ± Coversyl treatment arm had superior benefits to the atenolol ± thiazide combination, thereby creating the impression that this was due to some superiority inherent in the medicines rather than the blood pressure difference that was produced. The key message from ASCOT (and other hypertension studies) was that it was the amount by which blood pressure was lowered that was important rather than some other 'special' property of the medicine used.

The Panel noted that the ASCOT trial was established to determine whether, for a given reduction in blood pressure, newer antihypertensives (amlodipine ± perindopril) conferred any advantages over older agents (ß-blockers ± diuretics). Patients in both arms of the study had their treatment titrated to achieve target blood pressure (<140/90mmHg for patients without diabetes and <130/80mmHg for those with diabetes). The published results showed that, on average, in both treatment groups combined, blood pressure dropped from a mean 164/94.7mmHg to a mean 136.9/78.3mmHg ie an average reduction of 26.6/16.6mmHg. The Panel noted, however, that neither of the two bullet points at issue, 'BP was

reduced by 27/17mmHg in both treatment arms' and 'Average BP at the end of the study was: 137/78mmHg' stated that the results cited were from the combined patient groups; it appeared that the figures quoted applied to each treatment group separately which was not so. Blood pressure at the final visit was lower in the amlodipine ± perindopril arm than in the atenolol ± diuretic arm (136.1/77.4mmHg vs 137.7/79.2mmHg respectively representing mean falls of 27.5/17.7mmHg and 25.7/15.6mmHg). The average difference in blood pressure between the two groups throughout the trial was 2.7/1.9mmHg. The Panel considered that the bullet points were misleading in their portrayal of the blood pressure data from the ASCOT trial. In the Panel's view readers should have been told that blood pressure was lower in the amlodipine ± perindopril group than the other group so that the outcome data could be put into the correct clinical context and the impact of the differences understood. A breach of the Code was ruled.

A clinical effectiveness pharmacist at a local primary care trust (PCT), complained about a mailing (an outer wallet ref 06COASC117 and an 8 page booklet ref 06COASC117a) for Coversyl (perindopril) issued by Servier Laboratories Ltd. The wallet bore the statement 'News just in: The ASCOT results are OUT!'. The booklet, entitled 'The impact of the results of the ASCOT trial', summarised the study's design and results. ASCOT stood for Anglo Scandinavian Cardiac Outcomes Trial and compared combinations of atenolol ± thiazide diuretic vs amlodipine ± perindopril. The materials featured the Coversyl logo and the strapline 'Control hypertension. Reduce risk' throughout.

The complainant considered the content very misleading and the material needed to be withdrawn and a correction published. It appeared that the sponsorship of the ASCOT study by Servier (among others) had led to data being shared with the company. The inaccurate and inappropriate use of this data would lead to misinterpretation by busy clinicians and possibly lead to the increased use of amlodipine and perindopril for the treatment of hypertension without a full appraisal of the facts.

When writing to advise it of the complaint, the Authority asked Servier to consider the requirements of Clauses 7.2 and 7.4 of the Code.

1 Data Source

COMPLAINT

The complainant noted that the booklet was dated August 2005 and used data on file. By definition this could not then quote ASCOT trial data, as the trial was not published in The Lancet until September. This could therefore misrepresent the published trial data. As the complainant would go on to show, this had been borne out in the substance of this complaint.

RESPONSE

Servier noted the complainant's concern but noted that the mailing was not sent out until 5 September after the results of the ASCOT trial had been published.

PANEL RULING

The Panel noted that the material at issue, reporting the results of the ASCOT study, had been prepared in August 2005, the month before the results had been published in The Lancet. The data in the material was referenced to data on file. In the Panel's view it would not be unusual for study sponsors to be aware of results before they were published and to prepare material to coincide with publication. Use of data in this way was not misleading *per se*. The Panel ruled no breach of Clause 7.2 in this regard.

2 Claim 'There was also a trend towards a reduction in the combination of total CHD and non-fatal MI (the primary endpoint) in favour of amlodipine ± COVERSYL over atenolol ± bendroflumethiazide (4.5% vs. 4.9% p=0.11)'

COMPLAINT

The complainant stated that by definition there could be no 'trend' in statistics, a result was either significant or it was not. At p=0.11, it was not close to the arbitrary p=0.05 usually used to define statistical significance, so this was an invalid claim to make.

With regard to secondary outcome, the chart on page 4 of the booklet was different to the data presented in the ASCOT trial. The confidence intervals were not stated on the booklet representation, however the 'non-fatal MI (excl silent) and fatal CHD' appeared to cross the line of significance, whereas in the published paper the harm rate was quoted as 0.87 with a 95% CI of 0.76-1.00. The complainant therefore questioned the data source for this assertion as the two were at least not consistent and at worst incorrect.

RESPONSE

Servier noted the complainant's concerns but submitted that presenting results in this way was acceptable (and commonly done) in medical practice. As the complainant had focused on statistics Servier considered that he would be aware that the reason the primary endpoint was not statistically significant was because the trial was stopped early. However, nowhere did Servier actually claim statistical significance for the primary endpoint.

Servier had provided complete information regarding the primary endpoint and percentage reductions and p-values for all other endpoints in the results table. It was clear that even though not statistically significant the primary endpoint followed the same pattern or 'trend' as all the other endpoints. From the information provided it was very clear what the results of the ASCOT trial were and therefore Servier considered that this was not misleading.

The confidence interval line for non-fatal MI (excl silent) + fatal CHD did just cross the line of significance in the mailing (approximate CI at 1.02) and not in the publication (CI at 1.00). This was the result of a technical error in producing the piece and would be corrected in future materials. However, while Servier acknowledged that this meant that the figure was inaccurate, it did not consider that this error changed the overall results or messages and

conclusions that would be drawn from this table by the average reader. Servier therefore considered that this minor technical point did not render the results table misleading.

PANEL RULING

The Panel noted that the ASCOT study had not shown a statistically significant difference between amlodipine ± perindopril vs atenolol ± bendroflumethiazide with regard to decreased risk of total CHD and non-fatal MI. The Panel did not consider the claim that there was a trend in favour of amlodipine ± perindopril negated the impression that there was a statistically proven advantage for that regimen. The Panel considered that the claim was misleading in that regard. The Panel further considered that the misleading impression of the claim was strengthened by the claim 'Coversyl has something to celebrate: the ASCOT results' which appeared at the top of the page and the strapline 'Control hypertension. Reduce risk' which appeared at the bottom. A breach of Clause 7.2 was ruled.

With regard to the chart on page 4 of the booklet, the Panel noted that Servier had acknowledged that, due to a technical error, the results in the published paper had not been accurately reproduced. The result shown for non-fatal MI (excluding silent) + fatal CHD was thus inaccurate. A breach of Clause 7.2 was ruled.

3 Inaccurate use of blood pressure data

COMPLAINT

The complainant noted that in the booklet on page 4 'Clinical results' the following statements were made:

- BP was reduced by 27/17mmHg in both treatment arms
- Average BP at the end of the study was: 137/78mmHg.

Unfortunately, the crucial word 'combined' was missing. It should have stated in 'both treatment arms combined'. It clearly stated in the published paper that they were an average of both treatment arms combined. This was another clear indication that this was not based on the published study, as the booklet appeared to claim.

Immediately below these figures in the published paper it stated 'compared with those allocated the atenolol-based regimen, blood pressure values were lower throughout the trial in those allocated the amlodipine-based regimen. These differences were largest (5.9/2.4mmHg) at 3 months, and the average difference throughout the trial was 2.7/1.9mmHg'.

This information was not hard to miss and was crucial. The amlodipine-based regimen was better at lowering blood pressure than the atenolol-based regimen. This alone was likely to be the reason why there was a small reduction in secondary outcomes in the study, as expressed in the accompanying editorial. The wording in the booklet strongly suggested that there was no difference in blood pressure between the two treatment arms, which was obviously extremely misleading.

These misleading figures were then followed by a statement that the amlodipine ± Coversyl treatment arm had superior benefits to the atenolol ± thiazide combination, thereby creating the impression that this was due to some superiority inherent in the medicines used rather than the blood pressure difference that was produced. The key message from ASCOT (and other hypertension studies) was that what was important was the blood pressure lowering achieved rather than some other 'special' property of the medicine used.

RESPONSE

Servier noted that this complaint was virtually identical to that in Cases AUTH/1760/9/05, AUTH/1757/9/05 and AUTH/1759/9/05.

On page 4 of the booklet there was the heading 'Clinical results' with two bullet points: 'BP was reduced by 27/17mmHg in both treatment arms' and 'Average BP at the end of the study was: 137/78mmHg'. These bullet points clearly demonstrated to the reader that blood pressure targets had been achieved in both treatment groups (ie <140/90mmHg as described on page 3 of the booklet).

The ASCOT study was not designed to demonstrate superiority of one treatment regimen over another in terms of blood pressure lowering. Both treatment regimens were titrated to meet blood pressure target. The target in the ASCOT study was that both treatment groups reached the target of <140/90mmHg. The two bullet points simply informed the reader that blood pressures were lowered by similar amounts in both groups and met the pre-defined target set in the study protocol. Leading cardiologists described blood pressures in the two treatment groups in the ASCOT trial as 'virtually identical' and 'evenly matched' (ASCOT investigators 2005).

Although there was a small difference in blood pressures between the two treatment groups this could not account for the differences in endpoint reductions and Servier did not consider that the way this data had been presented was misleading or not capable of substantiation. If the bullet points had been presented differently informing readers of the small differences in blood pressure the results and messages conveyed by this mailing would still be the same. For example the ASCOT study investigators in the study publication (Lancet 2005) stated that the average blood pressure difference between the two groups would be expected to generate a difference of only 4-8% in coronary events and 11-14% in stroke. For information there was a 16% decrease in coronary events and a 23% decrease in stroke, therefore the small difference in blood pressure between the two treatment groups did not explain the difference in cardiovascular events.

Servier considered that this mailing did what it was designed to do, namely to provide health professionals with a 'Study summary' which clearly conveyed 'The impact of the results of the ASCOT trial'. Servier therefore considered that, with the exception of the technical error acknowledged above, this piece was not in breach of the Code.

PANEL RULING

The Panel noted that the ASCOT trial was established to determine whether, for a given reduction in blood pressure, newer antihypertensives (amlodipine ± perindopril) conferred any advantages over older agents (ß-blockers ± diuretics). Patients in both arms of the study had their treatment titrated to achieve target blood pressure (<140/90mmHg for patients without diabetes and <130/80mmHg for those with diabetes). The published results showed that, on average, in both treatment groups **combined**, blood pressure dropped from a mean 164/94.7mmHg to a mean 136.9/78.3mmHg ie an average reduction of 26.6/16.6mmHg. The Panel noted, however, that neither of the two bullet points at issue, 'BP was reduced by 27/17mmHg in both treatment arms' and 'Average BP at the end of the study was: 137/78mmHg' stated that the results cited were from the **combined** patient groups; it appeared that the figures quoted applied to each treatment group separately which was not so. Blood pressure at the final visit was lower in the amlodipine ± perindopril arm than in the atenolol ± diuretic arm (136.1/77.4mmHg vs 137.7/79.2mmHg respectively representing mean falls of 27.5/17.7mmHg and 25.7/15.6mmHg). The average difference in blood pressure between the two groups throughout the trial was 2.7/1.9mmHg. The Panel considered that the bullet points were misleading in their portrayal of the blood pressure data from the ASCOT trial. In the Panel's view readers should have been told that blood pressure was lower in the amlodipine ± perindopril group than the other group so that the outcome data could be put into the correct clinical context and the impact of the differences understood. A breach of Clause 7.2 was ruled.

Complaint received	**3 October 2005**
Case completed	**21 November 2005**

CASE AUTH/1764/10/05

GENERAL PRACTITIONER v SERVIER

Coversyl journal advertisement

A general practitioner complained about a journal advertisement for Coversyl (perindopril) issued by Servier. The advertisement stated 'ASCOT is the latest of 3 eminent trials to demonstrate the benefits of COVERSYL for patients with hypertension' and then mentioned the EUROPA study. The complainant alleged that this misleadingly implied that the EUROPA study had shown that Coversyl benefited patients with hypertension whereas the study actually looked at secondary prevention of coronary events in patients who had coronary heart disease.

The Panel noted that beneath the heading 'Coversyl can …' the first claim read 'ASCOT is the latest of 3 eminent trials to demonstrate the benefits of COVERSYL for patients with hypertension'. The second claim, ie the claim at issue, read 'The preliminary results of ASCOT, in addition to EUROPA and PROGRESS, prove that BP lowering with Coversyl 4-8mg can reduce the risk of a CV event'. The product logo appeared immediately below the second claim and immediately above the strapline 'Control hypertension. Reduce risk'. In the Panel's view the advertisement was about the benefits of treating hypertension. The two claims together implied that ASCOT, EUROPA and PROGRESS had each shown a benefit for Coversyl. The Panel considered that the claim at issue would be read by the majority as implying that the ASCOT data added to a pre-existing body of data (EUROPA and PROGRESS) which showed that antihypertensive therapy with Coversyl could reduce the risk of a CV event.

The Panel noted that the EUROPA study was designed to assess whether perindopril reduced cardiovascular risk in a low-risk population with stable coronary heart disease and no apparent heart failure. According to a table of baseline characteristics only 27% of patients in the perindopril group were hypertensive. All patients in EUROPA received 8mg perindopril; if this dose was not tolerated it could be reduced to 4mg. The dose of perindopril was thus adjusted according to tolerability and not according to blood pressure response. The Panel considered that within the context of an advertisement about the benefit of treating hypertension the reference to the EUROPA trial was misleading as alleged. A breach of the Code was ruled.

A general practitioner complained about a journal advertisement (ref 05COAD424) for Coversyl (perindopril) issued by Servier Laboratories Ltd.

COMPLAINT

The complainant noted that the advertisement stated 'ASCOT is the latest of 3 eminent trials to demonstrate the benefits of COVERSYL for patients with hypertension'. The EUROPA study was then mentioned. The implication that the complainant took from this was that Coversyl had been proven by the EUROPA trial to be of benefit to all patients with hypertension. Actually the EUROPA trial looked at secondary prevention of coronary events in patients who had proven coronary heart disease. As such, the complainant considered this advertisement was, at least, a deliberate attempt to mislead. Some might describe it as a lie.

When writing to Servier, the Authority asked it to respond in relation to Clause 7.2 of the Code.

RESPONSE

Servier noted that the advertisement had two claims below the heading 'Coversyl can…'.

The first claim stated 'ASCOT is the latest of 3 eminent trials to demonstrate the benefits of COVERSYL for patients with hypertension'. It was clear from the ASCOT study that if blood pressure was reduced in patients with hypertension the risk of cardiovascular events was reduced and therefore this claim was accurate and not misleading.

The complainant focused on the EUROPA study which was mentioned in the second claim 'The preliminary results of ASCOT, in addition to EUROPA and PROGRESS, prove that BP lowering with Coversyl 4-8mg can reduce the risk of a CV event'. In EUROPA Coversyl was shown to effectively reduce blood pressure compared to placebo and by reducing blood pressure reduced the risk of a cardiovascular event. Therefore the results of EUROPA proved that lowering blood pressure with Coversyl 4-8mg could reduce the risk of a cardiovascular event.

Servier submitted that the claim at issue was thus accurate and not misleading; Servier denied a breach of the Code.

PANEL RULING

The Panel noted that beneath the heading 'Coversyl can …' the advertisement read 'ASCOT is the latest of 3 eminent trials to demonstrate the benefits of COVERSYL for patients with hypertension'. The second claim, ie the claim at issue, read 'The preliminary results of ASCOT, in addition to EUROPA and PROGRESS, prove that BP lowering with Coversyl 4-8mg can reduce the risk of a CV event'. The product logo appeared immediately below the second claim and immediately above the strapline 'Control hypertension. Reduce risk'. In the Panel's view the advertisement was about the benefits of treating hypertension. The two claims together implied that ASCOT, EUROPA and PROGRESS had each shown a distinct benefit for Coversyl. The Panel considered that the claim at issue would be read by the majority as implying that the ASCOT data added to a pre-existing body of data (EUROPA and PROGRESS) which showed that antihypertensive therapy with Coversyl 4-8mg could reduce the risk of a CV event.

The Panel noted that the EUROPA study was designed to assess whether perindopril reduced cardiovascular risk in a low-risk population with stable coronary heart disease and no apparent heart failure. According to a table of baseline characteristics only 27% of patients in the perindopril group were hypertensive ie defined as those with blood pressure > 160/95mmHg or receiving antihypertensive treatment. All patients in EUROPA received 8mg perindopril; if this dose was not tolerated it could be reduced to 4mg. The dose of perindopril was thus adjusted according to tolerability and not according to blood pressure response. The Panel considered that within the context of an advertisement about the benefit of treating hypertension the reference to the EUROPA trial was misleading as alleged. A breach of Clause 7.2 was ruled.

Complaint received **5 October 2005**

Case completed **21 November 2005**

CASE AUTH/1765/10/05

GENERAL PRACTITIONER v PFIZER

Lipitor advertisement

A general practitioner complained that an advertisement for Lipitor (atorvastatin), issued by Pfizer, which had appeared as a 'Post-it Note' on the front cover of MIMS, did not contain prescribing information.

The Panel noted that the advertisement was detachable and was of the view that, given its format, the advertisement was a loose insert. As such the advertisement could not be an abbreviated advertisement and was required by the Code to include prescribing information. The Panel therefore ruled a breach of the Code, as acknowledged by Pfizer.

A general practitioner complained about an advertisement (ref LIP 1738T) for Lipitor (atorvastatin) issued by Pfizer Limited which had appeared as a 'Post-it Note' on the front cover of MIMS, September 2005.

COMPLAINT

The complainant noted that the advertisement did not contain prescribing information although it stated that further information was available from Pfizer. The advertisement mentioned the licensed indications for Lipitor. The complainant alleged a breach of the Code due to the absence of prescribing information.

When writing to Pfizer, the Authority asked it to respond in relation to Clauses 4.1 and 5.2 of the Code.

RESPONSE

Pfizer accepted that the advertisement was in breach of Clauses 4.1 and 5.2; it was not an abbreviated advertisement and therefore required the addition of prescribing information. The company had withdrawn the advertisement and would amend any future version to ensure compliance with the Code.

PANEL RULING

The Panel noted that the advertisement was stuck to the front cover of MIMS in the manner of a 'Post-it Note'. It was detachable and could easily be removed and replaced or stuck elsewhere. The Panel's view was that given its format the advertisement was a loose insert. It was not bound in or permanently fixed in some other way. The Panel noted Clause 5.2 of the Code that a loose insert in a professional publication could not be an abbreviated advertisement. The Panel considered therefore that the advertisement could not be an abbreviated advertisement. The prescribing information as required by Clause 4.1 of the Code should have been included. The Panel therefore ruled a breach of Clause 4.1 of the Code. The Panel noted that Pfizer had acknowledged that the advertisement in question was in breach of the Code as alleged.

Complaint received	**5 October 2005**
Case completed	**10 November 2005**

CASE AUTH/1768/10/05

PROCTER & GAMBLE v SHIRE

Colazide leavepiece

Procter & Gamble complained about a comparison of its product Asacol (mesalazine) with Colazide (balsalazide) which appeared in a leavepiece issued by Shire. Both medicines were for the treatment of ulcerative colitis.

Procter & Gamble referred to the claims 'Colazide controls ulcerative colitis longer than Asacol' and 'keeps patients in remission longer than Asacol' and noted that Green *et al* (1998b) concluded that both products were equally effective at maintaining remission at 12 months.

The Panel noted that Green *et al* (1998b), to which both of the claims were referenced, had compared the efficacy and safety of Colazide with Asacol in maintaining remission of ulcerative colitis over 12 months. At three months more patients in the Colazide group remained in remission than in the Asacol group (79% vs 65% p=ns). At 12 months 58% of patients in each treatment group remained in remission. The Panel considered that, on the basis of Green *et al* (1998b) there was no data to show that Colazide kept patients in remission longer than Asacol and that the claim 'keeps patients in remission longer than Asacol' was thus misleading and had not been substantiated. Breaches of the Code were ruled.

The Panel considered that 'Colazide controls ulcerative colitis longer than Asacol' was a very broad claim; it was unclear as to what was meant by 'control' and there was no indication as to the length of time over which 'control' had been assessed. Green *et al* (1998b) contained diary card data for the first three months of treatment which showed that certain symptoms were better controlled by Colazide than by Asacol eg nocturnal symptoms, whereas other symptoms eg stool frequency, were the same in both groups. There was no diary card data beyond three months. Only the lowest maintenance doses of each medicine had been used. The Panel considered that the unqualified claim 'Colazide controls ulcerative colitis longer than Asacol' was misleading and could not be substantiated. Breaches of the Code were ruled.

Procter & Gamble stated that the reference cited in support of the claim 'Colazide gets UC patients into remission faster than Asacol, and keeps UC under control longer' (Green *et al* 1998a) was based on patients with moderate to severe disease. Neither Asacol nor Colazide, however, were indicated in severe ulcerative colitis. In a study not cited in the leavepiece there was no significant difference between Colazide and Asacol in patients with mild to moderate ulcerative colitis. Further Green *et al* (1998a) stated that after 12 months, 58% of patients were still in remission irrespective of taking Colazide or Asacol.

The Panel noted that the claim in question was referenced to Green *et al* (1998b) and Green *et al* (1998a). With regard to the findings of Green *et al* (1998b) the Panel considered that its comments above were relevant. Green *et al* (1998a) had compared the efficacy and safety of Colazide with Asacol in acute ulcerative colitis, including severe disease for which neither of the medicines were licenced. There was no sub-group analysis of only those patients with moderate disease. The Panel considered that on the basis of the data before it the claim 'Colazide gets UC patients into remission faster than Asacol, and keeps UC under control longer' was misleading and had not been substantiated. Breaches of the Code were ruled.

Procter & Gamble alleged that the claim 'Accuracy of delivery and superior efficacy in both achieving and maintaining remission may be why 61% of patients who failed on Asacol, succeeded on Colazide' could not be substantiated by the abstract cited (Pruitt *et al* 2002) or other references in the leavepiece. The abstract concluded that the delivery mechanism of Colazide might be why patients who failed on Asacol treatment benefited from Colazide. Despite the use of the word may the claim clearly suggested that Colazide had a more accurate delivery mechanism and a superior efficacy to Asacol.

The Panel noted that the claim offered possible reasons as to why Colazide therapy was successful in 61% of those who had previously failed on Asacol. The claim was qualified by the word 'may' but the Panel considered that this did not negate the impression that 'Accuracy of delivery and superior efficacy in both achieving and maintaining remission' had been proven to be the reasons. This was not so. With regard to achieving and maintaining remission and the 'superior efficacy' of Colazide, the Panel considered that its comments above were relevant. With regard to the implied better 'Accuracy of delivery' the Panel noted that oral mesalazine (released as the active metabolite from balsalazide) was an intestinal anti-inflammatory which acted locally on the colonic mucosa. The clinical effect of both Colazide and Asacol was thus dependent upon the amount of mesalazine reaching the site of inflammation. No data had been supplied to show that Colazide was any more accurate in delivering mesalazine to where it was needed in the bowel than Asacol. The Panel considered that the claim in question could not be substantiated. A breach of the Code was ruled.

Procter & Gamble Pharmaceuticals UK, Limited complained about a leavepiece (ref 033/0166) for Colazide (balsalazide) issued by Shire Pharmaceuticals Ltd. The leavepiece, entitled 'Relapse or Relax' compared treatment of ulcerative colitis with Colazide or Asacol (mesalazine). Procter & Gamble supplied Asacol.

Procter & Gamble stated that following inter-company correspondence Shire had agreed to withdraw the leavepiece but it had appeared on Shire's stand at the Crohn's Masterclass meeting in August. Shire accepted that it had offered to withdraw the item but it was awaiting Procter & Gamble's acknowledgement of acceptance of this offer. Despite this intent, however, the item was inadvertently included on Shire's stand at the meeting.

1 Claims 'Colazide controls ulcerative colitis longer than Asacol' and 'keeps patients in remission longer than Asacol'

COMPLAINT

Procter & Gamble stated that these claims suggested that patients on Colazide were kept in remission longer than patients on Asacol. No references or data to support this statement were cited in the leavepiece. One reference relating to controlling remission was presented (Green *et al* 1998b). This study used Asacol at its lowest indicated dose for maintenance of remission; however it concluded that Asacol and Colazide were equally effective in maintaining remission at 12 months.

RESPONSE

Shire stated that whilst the Code did not specifically require references to be cited in support of all claims, the claims at issue were clearly marked as being supported by Green *et al* (1998b).

Although the percentage of patients in remission at 12 months was similar, fewer patients in the Colazide treated group relapsed within 3 months than in the Asacol group. Colazide treated patients also experienced more asymptomatic nights and days, more symptom-free nights per week and fewer nights per week with blood on their stools or toilet paper, mucus with their stool or sleep disturbance due to symptoms during the first 3 months of treatment than those receiving Asacol. Colazide prevented more relapses during the first 3 months of treatment and controlled worrisome nocturnal symptoms more effectively. This indicated that the patients who were treated with Asacol experienced a breakthrough of ulcerative colitis symptoms and/or relapsed earlier than those treated with Colazide, indicating that Colazide controlled ulcerative colitis longer and kept patients in remission longer than Asacol. The authors concluded that 'The results also show a therapeutic advantage for balsalazide in delaying relapse and maintaining more complete remission'.

Green *et al* (1998b) used Asacol at its lowest indicated dose for maintenance of remission, it was not clear if Procter & Gamble was thus alleging an unfair comparison. However, the study used comparable dose regimens, ie the lowest indicated doses for maintenance therapy for both products (3g Colazide daily and 1.2g Asacol daily).

No specific clauses of the Code were cited in relation to this allegation, but as the spirit of it was very similar to that detailed in 2 point below, Shire assumed that the allegations of breaches of Clauses 7.2 and 7.4 referred to both matters.

Shire denied breaches of Clauses 7.2 and 7.4 but acknowledged that it needed to make a clear distinction between the data observed at 3 months and 12 months and it had already withdrawn the leavepiece on this basis.

PANEL RULING

The Panel noted that Procter & Gamble had not stated those clauses of the Code which were alleged to have been breached as required by Paragraph 5.1 of the Constitution and Procedure. Shire had nonetheless responded in relation to the requirements of Clauses 7.2 and 7.4 of the Code on the basis that the spirit of the complaint was similar to point 2 below in which Procter & Gamble had cited those clauses. The Panel thus decided to consider this point in relation to the requirements of Clauses 7.2 and 7.4.

The Panel noted that Green *et al* (1998b), to which both of the claims were referenced, had compared the efficacy and safety of Colazide (3g daily) with Asacol (1.2g daily) in maintaining remission of ulcerative colitis over 12 months. The licensed dose of Colazide for maintenance therapy was 3-6g daily and the comparable dose for Asacol was 1.2-2.4g daily; Green *et al* (1998b) had thus compared the lowest maintenance dose of each medicine. The study showed that at three months more patients in the Colazide group remained in remission than in the Asacol group (79% vs 65%) although the difference did not achieve statistical significance. At 12 months 58% of patients in each treatment group remained in remission. The Panel considered that, on the basis of Green *et al* (1998b) there was no data to show that Colazide kept patients in remission longer than Asacol. The Panel considered that the claim 'keeps patients in remission longer than Asacol' was thus misleading and that it had not been substantiated. Breaches of Clause 7.2 and 7.4 were ruled.

The Panel considered that the claim 'Colazide controls ulcerative colitis longer than Asacol' was a very broad claim; it was unclear as to what was meant by 'control' and there was no indication as to the length of time over which 'control' had been assessed. The claim was referenced to Green *et al* (1998b) which contained diary card data for the first three months of treatment to show that certain symptoms of ulcerative colitis were better controlled by Colazide than by Asacol eg nocturnal symptoms, whereas other symptoms eg stool frequency were the same in both groups. There was no diary card data beyond three months. Only the lowest maintenance doses of each medicine had been used. The Panel considered that the unqualified claim 'Colazide controls ulcerative colitis longer than Asacol' was misleading and could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

2 Claim 'Colazide gets UC patients into remission faster than Asacol, and keeps UC under control longer'

COMPLAINT

Procter & Gamble stated that the reference cited in support of the claim (Green *et al* 1998a) was based on a population of patients with moderate to severe ulcerative colitis. This patient population was therefore largely irrelevant as Asacol and Colazide were not indicated for the treatment of severe disease. Levine *et al* (2002) found, in a study not cited in the leavepiece, that there was no significant difference between Colazide and Asacol in patients with mild to moderate ulcerative colitis. Further, Green *et al* (1998a) stated that after 12 months 58% of the patients were still in remission irrespective of taking Colazide or Asacol.

Procter & Gamble alleged that the claims of faster action and longer control breached Clauses 7.2 and 7.4 of the Code.

RESPONSE

Shire stated that the majority (69%) of patients included in Green *et al* (1998a) had moderate colitis at baseline, and so Procter & Gamble's statement that the patient population was 'largely irrelevant' was neither accurate nor fair. Moreover, the classification of mild, moderate or severe disease in this study was based on the patients' overall evaluation of symptoms with regard to tolerability and interference with normal activities. This was a somewhat subjective and uncontrolled measure. Whilst a clinical assessment of disease extent was undertaken by sigmoidoscopy, no correlation between the sigmoidoscopic grades (0-4) and the subjective patient assessments was provided, although the authors stated 'The majority of patients had left-sided disease which was associated with grade 2 colitis and moderate symptoms'.

Results were provided with regard to remission status by sigmoidoscopic grade. The study showed that 72% of patients in the Colazide group with sigmoidoscopic grade 2 disease achieved remission after 12 weeks compared with 45% of patients in the Asacol group. However the published results did not allow distinction between onset of remission for patients with moderate disease from that in patients with severe disease classified by patients' evaluation of symptoms, and so Shire had already withdrawn the promotional piece on that basis.

Whilst the reference preferred by Procter & Gamble (Levine *et al*) referred to mild to moderate in its title, an analysis of the disease activity scores at entry for the patient population revealed between 6 and 55% of the patients were classified as 'severe' depending on the assessment used. This further illustrated the difficulty in classifying the severity of the disease, and lack of any consensus classification.

While Levine *et al* did not find a significant difference between Colazide and Asacol with regard to complete remission, five of the seven primary efficacy parameters favoured Colazide over Asacol, as did disease activity scores for rectal bleeding, sigmoidoscope scores and physician's global assessment. Levine *et al* also noted that the rate of onset of disease symptom improvements appeared to be more rapid with Colazide than Asacol. Therefore Shire did not believe that the overall results of this study changed the balance of evidence comparing the two treatments, nor that the study population was any more relevant to the licensed indication.

With regard to the use of Green *et al* (1998a) to support the claim 'Colazide … keeps UC under control longer', when 58% of patients were in remission at 12 months irrespective of taking Colazide or Asacol, Shire considered that this point has been adequately covered in point 1 above. Fewer patients in the Colazide treated group relapsed within 3 months than in the Asacol group.

Shire did not consider that the allegations of breaches of Clauses 7.2 and 7.4 were valid with respect to the above claims.

PANEL RULING

The Panel noted that the claim in question was referenced to Green *et al* (1998b) and Green *et al* (1998a). With regard to the findings of Green *et al* (1998b) the Panel considered that its comments at point 1 above were relevant. Green *et al* (1998a) had compared the efficacy and safety of Colazide with Asacol in acute ulcerative colitis; 30% of patients in the Colazide group had severe disease compared with 33% of those in the Asacol group. Both medicines, however, were only licensed for use in mild to moderate ulcerative colitis, they were not licensed for use in severe disease. Green *et al* (1998a) did not contain a sub-group analysis of only those patients with moderate disease. The Panel considered that on the basis of the data before it the claim 'Colazide gets UC patients into remission faster than Asacol, and keeps UC under control longer' was misleading and had not been substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

3 Claim 'Accuracy of delivery and superio efficacy in both achieving and maintaining remission may be why 61% of patients who failed on Asacol, succeeded on Colazide'

COMPLAINT

Procter & Gamble noted that this claim stated that Colazide had a more accurate delivery than Asacol and that Colazide had a superior efficacy to Asacol. Neither of these claims were substantiated in the abstract cited (Pruitt *et al* 2002) or other references in the leavepiece. The abstract concluded that the delivery mechanism of Colazide might be why patients who failed on Asacol treatment benefited from Colazide. Despite the use of the word *may* the statement clearly suggested that Colazide had a more accurate delivery mechanism and a superior efficacy to Asacol which was not substantiated by any of the references in the leavepiece. Procter & Gamble alleged that the claim breached Clause 7.4 of the Code.

In conclusion Procter & Gamble considered that the misleading nature of the leavepiece, as detailed above, and Shire's failure to honour its commitment should result in the immediate withdrawal of the leavepiece and any other promotional item containing the erroneous claims. In addition Shire should issue a non-promotional corrective statement to the doctors who had attended the meeting where the leavepiece had been available.

RESPONSE

Shire submitted that the above mentioned references, including that by Levine *et al*, cited by Procter & Gamble, more than adequately supported the claim of superior efficacy of Colazide over Asacol.

In considering the delivery mechanisms of the two treatments, the pharmacodynamic properties of the

active moiety, mesalazine (5-ASA), must be noted. As stated in the Colazide summary of product characteristics (SPC): 'mesalazine is an intestinal anti-inflammatory agent acting locally on the colonic mucosa'. Therefore, delivery of the active medicine to the site of action, whilst avoiding uptake of the medicine before it reached this site, was the primary purpose of the delivery mechanism. The delivery mechanism of Colazide involved bacterial cleavage of the molecule in the colon; the Colazide SPC stated 'systemic uptake of balsalazide itself is low (<1%) and the major part of the dose is split in the colon … [resulting in] the primary metabolites 5-ASA … and 4-ABA … an inert carrier'.

Thus, with less than 1% of the medicine being absorbed systemically, Shire submitted that it was justified in claiming an accurate delivery of the medicine to the colon. In contrast, the Asacol delivery mechanism was a pH-dependant release of mesalazine. The Asacol SPC stated that this release occurred in both the ileum and large bowel (colon). In fact, the reference cited by Procter & Gamble (Levine *et al*) also stated that the more rapid onset of action of Colazide compared with Asacol might by attributable to a greater amount of 5-ASA reaching the colon from the delivery mechanism of Colazide. Significantly higher steady-state plasma levels of 5-ASA and its metabolite were noted in the Asacol-treated patients than the Colazide-treated patients, despite equimolar dosing of 5-ASA, suggesting the possibility of pre-colonic absorption of 5-ASA with Asacol.

Therefore, Shire submitted that there was adequate substantiation of the claim that Colazide had a more accurate delivery mechanism than Asacol and that there was no breach of Clause 7.4.

PANEL RULING

The Panel noted that the claim offered possible reasons as to why Colazide therapy was successful in 61% of those who had previously failed on Asacol. The claim was qualified by the word 'may' but the Panel considered that this did not negate the impression that 'Accuracy of delivery and superior efficacy in both achieving and maintaining remission' had been proven to be the reasons. This was not so. With regard to achieving and maintaining remission and the 'superior efficacy' of Colazide, the Panel considered that its comments at point 1 above were relevant. With regard to the implied better 'Accuracy of delivery' the Panel noted that oral mesalazine (released as the active metabolite from balsalazide) was an intestinal anti-inflammatory which acted locally on the colonic mucosa. The clinical effect of both Colazide and Asacol was thus dependent upon the amount of mesalazine reaching the site of inflammation. No data had been supplied to show that Colazide was any more accurate in delivering mesalazine to where it was needed in the bowel than Asacol. The Panel considered that the claim in question could not be substantiated. A breach of Clause 7.4 was ruled.

Complaint received	**10 October 2005**
Case completed	**9 December 2005**

GAYS AGAINST GENOCIDE v GILEAD SCIENCES

Material on a website

A gay rights organisation, Gays Against Genocide, complained that clicking on the Gilead Sciences' logo on an open access website, www.Gay.com, took the reader to the home page of Gilead Sciences' American parent company which featured material about prescription only medicines for HIV. The complainant was particularly concerned that this link was available from a page where patients shared information and sought help and advice about HIV and treatment options. Direct advertising of specific medicines should not be part of the treatment decision making process.

The Panel noted that although Gilead Sciences had agreed to sponsor certain pages of Gay.com, an open access website aimed at the gay community, it had not seen or approved the pages which had been published. The web page publisher had independently decided to use Gilead Sciences' logo contrary to the company's previous instruction and had used its US website hyperlink without the company's knowledge or approval. The Panel noted that the publishers had acted unilaterally, prior to finalisation of the agreement between the parties, and not as the company's agents or otherwise on behalf of the company: Gilead Sciences was thus not responsible for the material at issue. No breach of the Code was ruled.

A gay rights organisation, Gays Against Genocide, complained about a link on an open access website, www.Gay.com sponsored by Gilead Sciences Limited to the home page of Gilead Sciences' American parent company which featured material about prescription only medicines.

COMPLAINT

The complainant noted that Gilead Sciences sponsored the 'Dear Doctor' page on Gay.com and although the company had stated that it had no editorial control over the content, two clicks on the Gilead Sciences logo took the reader to direct advertising of the company's HIV medicines. The complainant considered that this was illegal.

The complainant was further concerned since Gilead Sciences' logo appeared on the HIV forum where patients shared information and sought help and advice about HIV and treatment options. The complainant recognised that Gay.com had to make a profit but the HIV pages were a community resource. As a community resource, albeit in a profit making organisation's website, they had a responsibility to readers, particularly those who used the forum to get advice on HIV and treatment options. Direct glossy advertising of specific HIV medicines should not form part of any treatment decision making process. It was a route that the complainant considered one should not go down.

The complainant referred to the Health Select Committee fourth report on the Influence of the Pharmaceutical Industry 'The direct advertising of prescription drugs to patients is prohibited. Direct to consumer advertising (DTCA) of prescription only medicines is permitted only in the US and New Zealand. Moves towards extending DTCA to Europe proposed by the European Commission were quashed by the European Parliament in October 2002 by a majority of 494 to 42'.

The complainant requested that Gilead Sciences was censured and requested that the direct advertising of its HIV medicines was removed.

When writing to Gilead Sciences the Authority asked it to respond in relation to Clauses 20.1 and 21.1 of the Code.

RESPONSE

Gilead Sciences stated that it took the Code and the regulations on DTCA very seriously and was committed to complying with them.

Gilead Sciences had never attempted nor sanctioned DTCA or promotion of prescription only medicines (POMs) in the UK. Gay.com had used the Gilead Sciences logo and its US website hyperlink address without the company's knowledge or prior approval. Once aware of this mistake, Gilead Sciences immediately ensured that all potential DTCA with its name was immediately removed from the Gay.com website. Gilead Sciences would never wish to compromise its position with the patient community.

Gilead Sciences stated that it had always tried to explain to all external groups which it supported, such as Gay.com, the relevant aspects of the regulations governing the pharmaceutical industry. This included the regulations on DTCA in the UK.

Gilead Sciences explained that in August 2005 Gay.com asked the company for sponsorship for various health education initiatives under development on its website. Sponsorship for the health education initiatives of the Gay.com newsletter and of an online message board was subsequently agreed between the two parties. Gilead Sciences had explained to Gay.com the requirements of the Code in relation to its sponsorship. There was no intention from either Gay.com or Gilead Sciences, to promote Gilead Sciences' products either directly or indirectly through this sponsorship.

In order to acknowledge the nature of Gilead Sciences' sponsorship and to ensure that it was associated with educational content and that Gilead Sciences would have no further editorial control, it was agreed that Gay.com would design and submit a mock-up of the web pages under consideration for approval by Gilead Sciences prior to their publication. These mock-ups were sent to Gilead Sciences on 27 September 2005. Gilead Sciences did not approve the content nor the layout of these pages and on 3 October requested revisions be made. In particular

Gilead Sciences asked for the prominent company logo to be removed as this inferred that Gilead Sciences had editorial control of its content. In addition the company requested that the wording acknowledging sponsorship of the site be changed to read: 'Gilead Sciences Ltd is pleased to support the health initiatives of gay.com through an unrestricted educational grant. Gilead Sciences has no editorial control on the content of these pages'. Gilead Sciences requested that a full re-submission of the mock-ups, incorporating these amendments, be made before it gave its final approval. Gay.com agreed and resubmitted the pages by email on the 18 October 2005; these were pending approval.

On 10 October, prior to receiving a revised version of the mock-ups the UK Coalition (UKC) of People Living with HIV told Gilead Sciences that it had received a complaint that Gilead Sciences might be advertising medicines directly to patients on the website. It was noted by the UKC that Gilead Sciences' logo was also prominently displayed. Gilead Sciences assured the UKC that it was not aware that this had occurred and that it had been done without the knowledge or agreement of the company. Gilead Sciences undertook to investigate this immediately.

Gilead Sciences immediately contacted Gay.com and it confirmed that the web page had gone live and included Gilead Sciences' logo, which it had copied from Gilead Sciences' US website and included the hyperlink to that website. Gilead Sciences demanded that its logo and the web page be removed with immediate effect and that this be confirmed in writing. The company also insisted that an apology be posted on the Gay.com website to Gay.com readers. Gilead Sciences immediately informed the UKC of the actions to be undertaken by Gay.com to correct the mistake. Gilead Sciences confirmed that the web pages had been removed within one hour of it contacting Gay.com.

Written confirmation of the removal of the web pages was received on the 11 October 2005 together with an admission that this had been an error on the part of Gay.com, and that it accepted full responsibility (a copy was provided). Gay.com also posted an apology to its readers on its website message boards and sent someone who had complained to it about this matter an e-mail explaining and apologising for the error, a copy of which was provided.

In summary, Gilead Sciences remained unaware of the publication of its logo or the hyperlink to its US website on Gay.com before the mistake was highlighted. Gilead Sciences took immediate steps to rectify this situation as soon as it was brought to its attention. Furthermore, Gilead Sciences remained in communication with Gay.com to ensure this error did not occur again and it had re-iterated the requirements of the Code. Gilead Sciences remained committed to fully complying with the Code.

PANEL RULING

The Panel noted that Gilead Sciences had agreed to sponsor certain pages of an open access website aimed at the gay community. The company had amended the initial mock-ups of the pages and asked for them to be resubmitted for approval prior to publication. On 10 October, before the revised mock-ups had been resubmitted, Gilead Sciences was notified that the web pages at issue had been published and included the company's logo and a hyperlink to the company's American parent website which featured promotion of prescription only medicines, including the HIV product, Truvada.

The Panel noted that Gilead Sciences had not seen or approved the pages which had been published. The web page publisher had independently decided to use Gilead Sciences' logo contrary to the company's previous instruction that it should be removed and had used its US website hyperlink without the company's knowledge or approval. The Panel noted that the publishers had acted unilaterally, prior to finalisation of the agreement between the parties and were thus not acting as the company's agents or otherwise on behalf of the company: Gilead Sciences was thus not responsible for the material at issue. No breach of Clauses 20.1 and 21.1 was ruled.

Complaint received	**12 October 2005**
Case completed	**14 December 2005**

GAYS AGAINST GENOCIDE v ABBOTT

Advertisement in Positive Nation magazine

A gay rights organization, Gays Against Genocide, complained about an advertisement placed by Abbott in Positive Nation magazine. Positive Nation was published monthly and distributed widely throughout the UK by the UK Coalition (UKC) of People Living with HIV and AIDS, a national patient group.

The complainant explained that ten years could elapse between infection with HIV and the need for medication. As there were no set rules about when to start treatment the advertisement was designed to persuade and pressurise people who were HIV positive to ask their doctors for treatment.

The complainant was also concerned that people who were HIV positive must adopt a healthy lifestyle if they were to maintain good health. The advertisement implied that a person's full health was taken care of resulting in those exposed to it not adopting a more healthy lifestyle.

The Panel noted that the advertisement featured the photograph of a hand holding a red ribbon, a symbol associated with World AIDS Day. Text beneath read 'In their hands it's a sign of awareness. In your hands it's a sign of understanding. In our hands it's a sign of commitment'. The Abbott logo appeared in the bottom right hand corner above 'HIV Care for the duration'.

The advertisement made no reference, actual or implied to any specific medicines or treatments for HIV. The Panel considered that the advertisement raised awareness of Abbott's corporate interest in the therapy area. It might facilitate the market development of Abbott's products. Nonetheless the Panel did not consider that the advertisement constituted an advertisement for a specific medicine to the general public. No breach of the Code was ruled.

The Panel did not consider that the advertisement raised unfounded hopes of successful treatment such that readers would be encouraged not to adopt a healthy lifestyle. No breach of the Code was ruled.

A gay rights organization, Gays Against Genocide, complained about an advertisement (ref HXKAL2005565) placed by Abbott Laboratories Limited in the August and October 2005 editions of Positive Nation magazine. Positive Nation was published monthly by the UK Coalition (UKC) of People Living with HIV and AIDS, a national patient group which informed, campaigned, researched and advocated for people with HIV. The magazine was widely distributed throughout the UK.

COMPLAINT

The complainant explained that the time between infection with HIV and the need for medication could be as long as ten years. As there were no set rules by the medical profession about when to start treatment the advertisement was designed to persuade people who were HIV positive to ask their doctors for treatment. The advertisement was clearly meant to pressurise people.

The complainant was also concerned that people who were HIV positive must adopt a healthy lifestyle if they were to maintain good health. The advertisement clearly implied that a person's full health was taken care of resulting in people exposed to it not adopting a more healthy lifestyle.

The complainant hoped that his complaint would lead to a ban on all future advertising in Positive Nation and by pharmaceutical companies to people who were HIV positive. Being HIV positive was a vulnerable and fearful time and patients should consult and discuss treatment with their clinicians without this sort of pressure.

RESPONSE

Abbott wished to reassure the complainant that it was not the intention of the advertisement to pressurise anyone into asking their doctors to prescribe medication.

There was no mention in the advertisement of any specific treatment paradigm that might be used when an individual had been diagnosed with HIV/AIDS. In particular, the advertisement did not mention any medicine by name, nor did it mention any particular class of medicine. Nor was there any statement that could be construed as urging the reader to contact their doctor, for whatever reason. Abbott denied therefore any breach of Clauses 20.1 or 20.2 of the Code.

The red ribbon featured in the advertisement was a symbol associated with World AIDS Day, supported in the UK by the National Aids Trust; it was as a sign of support for people living with HIV and a symbol of hope for the future. The representation of the ribbon within the corporate advertisement highlighted Abbott's continued support for people living with HIV.

Abbott noted that its support for people living with HIV went beyond the development and distribution of effective antiretroviral medications. Abbott had invested $100 million over five years in the fight against HIV/AIDS through various programs that addressed areas of critical need in developing countries.

Finally, Abbott noted that funding from the advertisement contributed to the production of Positive Nation magazine and to the work of UKC.

PANEL RULING

The Panel noted that the advertisement featured the photograph of a hand holding a red ribbon, a symbol associated with World AIDS Day. Text beneath read

'In their hands it's a sign of awareness. In your hands it's a sign of understanding. In our hands it's a sign of commitment'. The Abbott logo appeared in the bottom right hand corner above 'HIV Care for the duration'.

Clause 20.1 of the Code stated, *inter alia*, that prescription only medicines must not be advertised to the general public. The Panel noted that the advertisement made no reference, actual or implied to any specific medicines or treatments for HIV. The Panel considered that the advertisement raised awareness of Abbott's corporate interest in the therapy area. It might facilitate the market development of Abbott's products. Nonetheless the Panel did not consider that the advertisement constituted an advertisement for a specific medicine to the general public. No breach of Clause 20.1 was ruled.

The Panel noted the requirements of Clause 20.2 of the Code that information about medicines which was made available to the general public must be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. 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 accepted that the advertisement might raise awareness of Abbott's commercial interest in this therapeutic area but it did not encourage patients to ask their doctor to prescribe a specific medicine. The Panel did not consider that the advertisement raised unfounded hopes of successful treatment such that readers would be encouraged not to adopt a healthy lifestyle. The Panel ruled no breach of Clause 20.2 of the Code.

Complaint received **19 October 2005**

Case completed **18 November 2005**

CASE AUTH/1773/10/05 *NO BREACH OF THE CODE*

GAYS AGAINST GENOCIDE v BRISTOL-MYERS SQUIBB

Advertisement in Positive Nation magazine

A gay rights organization, Gays Against Genocide, complained about an advertisement placed by Bristol-Myers Squibb in Positive Nation magazine. Positive Nation was published monthly and distributed widely throughout the UK by the UK Coalition (UKC) of People Living with HIV and AIDS, a national patient group.

The complainant explained that ten years could elapse between infection with HIV and the need for medication. As there were no set rules about when to start treatment the advertisement was designed to persuade and pressurise people who were HIV positive to ask their doctors for treatment.

The complainant also noted that people who were HIV positive must adopt a healthy lifestyle if they were to maintain good health. The advertisement implied that a person's full health was taken care of resulting in those exposed to it not adopting a more healthy lifestyle.

The Panel noted that the advertisement featured a group photograph of five people. In the top right hand corner of the advertisement was 'BMS Virology' in logo type with the statement 'Bristol-Myers Squibb Company' beneath. The only other text was the headline which ran along the bottom edge and read 'inspired by the SPIRIT of people with HIV'. There was no reference to medicines or treatments for HIV. Bristol-Myers Squibb had placed the advertisement and marketed treatment for those with AIDS. The Panel considered that the advertisement raised awareness of Bristol-Myers Squibb's corporate interest in the therapy area. The advertisement might facilitate the market development of Bristol-Myers Squibb's products. Nonetheless the Panel did not consider that the advertisement advertised a medicine to the general public. No breach of the Code was ruled.

The Panel accepted that the advertisement might encourage patients to discuss Bristol-Myers Squibb's products with their doctor but it did not encourage patients to ask their doctor to prescribe a specific medicine. The Panel did not consider that the advertisement raised unfounded hopes of successful treatment such that readers would be encouraged not to adopt a healthy lifestyle. No breach of the Code was ruled.

A gay rights organization, Gays Against Genocide, complained about an advertisement (ref HIV/0243ad) placed by Bristol-Myers Squibb Pharmaceuticals Limited in the August and October 2005 editions of Positive Nation magazine. Positive Nation was published monthly by the UK Coalition (UKC) of People Living with HIV and AIDS, a national patient group informing, campaigning, researching and advocating for people with HIV. The magazine was widely distributed throughout the UK to those living with HIV and AIDS.

COMPLAINT

The complainant noted that the time between infection with HIV and the need for medication could be as long as ten years. As there were no set rules by the medical profession about when to start treatment the advertisement was designed to persuade people who were HIV positive to ask their doctors for treatment. The advertisement was clearly meant to pressurise people.

The complainant further noted that people diagnosed HIV positive must adopt a healthy lifestyle if they were to maintain good health. The advertisement at issue clearly implied that a person's full health was taken care of resulting in those exposed to it not adopting a more healthy lifestyle.

The complainant hoped his complaint would lead to a ban on all future advertising in Positive Nation by pharmaceutical companies to people who were HIV positive. Being HIV positive was a vulnerable and fearful time and patients should consult and discuss treatments with their clinicians without this sort of pressure.

When writing to Bristol-Myers Squibb, the Authority asked it to respond in relation to Clauses 20.1 and 20.2 of the Code.

RESPONSE

Bristol-Myers Squibb stated that the advertisement made no mention of any medicine and made no promotional claims which would encourage a patient to approach their doctor to obtain HIV therapy. The advertisement was a general promotional piece in the HIV therapeutic area designed to raise awareness of the company. Bristol-Myers Squibb denied a breach of Clause 20.1 of the Code.

Bristol-Myers Squibb noted that the advertisement provided no information or claims on any products. There were no claims of therapy efficiency or safety of any of the company's products. Bristol-Myers Squibb denied a breach of Clause 20.2 of the Code.

Bristol-Myers Squibb noted that there were no references or claims in the advertisement as to when therapy should be initiated. The company refuted the allegation that the advertisement was designed to pressurize people.

The company further noted that there were no claims in the advertisement regarding patients' existing lifestyle (or need to alter it), nor any all embracing claims that HIV treatment would result in better health. In fact, there were no claims in the advertisement.

Bristol-Myers Squibb stated that Positive Nation was a UK HIV and sexual health magazine published by the UKC. The company was pleased to support Positive Nation and its continued activities within the scope of the Code.

PANEL RULING

The Panel noted that the advertisement featured a group photograph of a group of five people. In the top right hand corner was 'BMS Virology' in logo type with the statement 'Bristol-Myers Squibb Company' beneath. The only other text was the headline which ran along the bottom edge and read 'inspired by the SPIRIT of people with HIV'. There was no reference in the advertisement to medicines or treatments for HIV. The Panel noted that Clause 20.1 of the Code stated that prescription only medicines (POMs) and certain pharmacy medicines must not be advertised to the general public. Bristol-Myers Squibb had placed the advertisement and marketed treatment for those with AIDS. The Panel considered that the advertisement raised awareness of Bristol-Myers Squibb's corporate interest in the therapy area. The advertisement might facilitate the market development of Bristol-Myers Squibb's products. Nonetheless the Panel did not consider that the advertisement advertised a medicine to the general public. No breach of Clause 20.1 was ruled.

The Panel noted the requirements of Clause 20.2 of the Code that information about medicines which was made available to the general public must be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. 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 accepted that the advertisement might encourage patients to discuss Bristol-Myers Squibb's products with their doctor but it did not encourage patients to ask their doctor to prescribe a specific medicine. The Panel did not consider that the advertisement raised unfounded hopes of successful treatment such that readers would be encouraged not to adopt a healthy lifestyle. The Panel ruled no breach of Clause 20.2 of the Code.

Complaint received **19 October 2005**

Case completed **21 November 2005**

CASE AUTH/1774/10/05

GAYS AGAINST GENOCIDE v GILEAD SCIENCES

Advertisement in Positive Nation magazine

A gay rights organization, Gays Against Genocide, complained about an advertisement placed by Gilead Sciences in Positive Nation magazine. Positive Nation was published monthly and distributed widely throughout the UK by the UK Coalition (UKC) of People Living with HIV and AIDS, a national patient group.

The complainant noted that ten years could elapse between infection with HIV and the need for medication. As there were no set rules about when to start treatment the advertisement was designed to persuade and pressurise people who were HIV positive to ask their doctors for treatment.

The complainant was also concerned that people who were HIV positive must adopt a healthy lifestyle if they were to maintain good health. The advertisement clearly implied that a person's full health was taken care of resulting in those exposed to it not adopting a more healthy lifestyle.

The Panel noted that the advertisement featured a montage of photographs of people, places and things. The headline 'creating confidence in everyday life' was followed by 'HIV treatments have made a huge difference to people's lives, but they can limit the ability to carry on with daily life. To live your life with confidence, Gilead aims to provide products that are convenient and effective'. A strapline in the bottom right hand corner stated 'everyday life'. The advertisement also featured Gilead Sciences' company logo which incorporated the company's US website address (www.gilead.com). Gilead Sciences had placed the advertisement in question and marketed treatment for those with AIDS. The Panel considered that the advertisement raised awareness of the company's corporate interest in the therapy area. The advertisement might facilitate the market development of Gilead Sciences' products. Nonetheless the Panel did not consider that the advertisement advertised a medicine to the general public. No breach of the Code was ruled.

The advertisement included the US website address www.gilead.com which immediately took the reader to a page on a US website which featured three HIV therapies, Truvada, Emtriva and Viread. A fourth product, Hepsera for the treatment of chronic hepatitis C, was also featured.

The advertisement implied that Gilead Sciences provided products which were convenient and effective as opposed to other products which limited a person's ability to carry on with daily life. On balance the Panel considered that the advertisement would encourage HIV patients to ask their doctors to prescribe at least one of the four specific medicines referred to on the website. A breach of the Code was ruled. The Panel, however, did not consider that the advertisement raised unfounded hopes of successful treatment such that readers would be encouraged not to adopt a healthy lifestyle. No breach of the Code was ruled.

A gay rights organization, Gays Against Genocide, complained about an advertisement (ref 162/UKM/03-10/05) placed by Gilead Sciences Limited in the August and October 2005 editions of Positive Nation magazine. Positive Nation was published monthly by the UK Coalition (UKC) of People Living with HIV and AIDS, a national patient group informing, campaigning, researching and advocating for people with HIV. The magazine was widely distributed throughout the UK to those living with HIV and AIDS.

COMPLAINT

The complainant noted that the time between infection with HIV and the need for medication could be as long as ten years. As there were no set rules by the medical profession about when to start treatment the advertisement was designed to persuade people who were HIV positive to ask their doctors for treatment. The advertisement was clearly meant to pressurise people.

The complainant further noted that people diagnosed HIV positive must adopt a healthy lifestyle if they were to maintain good health. The advertisement clearly implied that a person's full health was taken care of resulting in those exposed to it not adopting a more healthy lifestyle.

The complainant hoped his complaint would lead to a ban on all future advertising in Positive Nation by pharmaceutical companies to people who were HIV positive. Being HIV positive was a vulnerable and fearful time and patients should consult and discuss treatments with their clinicians without this sort of pressure.

When writing to Gilead Sciences, the Authority asked it to respond in relation to Clauses 20.1 and 20.2 of the Code.

RESPONSE

Gilead Sciences stated that it had not intended to by-pass or replace the essential and confidential therapeutic relationship of patients and their health professionals nor had it intended to pressurize patients, either directly or indirectly, to take treatments or to ask their health professionals for any specific medicine.

The advertisement was intended to celebrate the great advances that had been made in HIV treatment; developments that since the discovery of the HIV virus in the early 1980s had significantly improved the lives of people and reduced the morbidity and mortality of those so infected. The advertisement was also intended to communicate the company's strong and ongoing commitment to research and development into further improvements of treatments for HIV.

The title of the advertisement, 'Creating confidence in everyday life', was followed by: 'HIV treatments have

made a huge difference to people's lives, but they can limit the ability to carry on with everyday life'. These statements were substantiated by Eggert *et al* (2002) who analysed the prognosis of HIV infection before and after the advent of highly active antiretroviral treatment (HAART) and showed that the 3-year probability of disease progression was greater in the pre-HAART era than it was in the HAART period, at any CD4 count and viral load studied. Furthermore, the Public Health Laboratory Service had published epidemiological data of the rates of diagnoses of AIDS and death in the UK population. Since 1995-1996, when HAART became widely available, the rates of diagnoses of AIDS and death had markedly reduced.

Despite the great improvements in the prognosis of HIV infection, the current British HIV Association (BHIVA) guidelines noted that 'with currently available antiretroviral agents, eradication of HIV infection is not likely to be possible. The main aim of treatment is thus to prolong and improve quality of life by maintaining suppression of virus replication for as long as possible'. The BHIVA guidelines also recognised that 'the leading determinant of a successful and durable virological and immunological responses to HAART is adherence sustained without lapse at extraordinarily high levels for many years'. Gilead Sciences noted that adherence was impaired by the toxicity that could be experienced with any treatment and by the patient's inability to successfully integrate the treatment into daily life.

Gilead Sciences considered that the statements used in its advertisement were factual, substantiable and presented in a balanced way. Furthermore, the company considered that they did not raise unfounded hopes of successful treatment or were misleading with regard to safety in this therapeutic area.

A further paragraph in the advertisement stated: 'To live your life with confidence, Gilead aims to provide products that are convenient and effective'. There was an ongoing need in all areas of medicine for continuing to develop and refine treatments which were both effective and convenient to take. This statement was intended to represent the company's research and development aims. Gilead Sciences had not intended either directly or indirectly, to encourage patients to seek any specific medicine and strongly considered that the decision to start HAART, or the choice of HAART remained wholly within the confidential therapeutic environment of patients and their health professionals. The company denied a breach of either Clause 20.1 or 20.2.

Nevertheless, Gilead Sciences noted that prior to receiving this complaint, it had changed its advertisement and as a result, the advertisement at issue was no longer in use. In the light of the complainant's interpretation of the advertisement, and so that it could not be misconstrued, Gilead Sciences had also decided that advertisements which would appear in future issues of Positive Nation would not refer to the company's aims for its HIV research and development programme and the website address, which was previously part of its logo, would be removed.

Gilead Sciences noted that the images in its advertisement were meant to represent people living and enjoying their lives, without any implication that those people were taking or not taking treatments. Thus, the images were meant to be inclusive and represent a sense of 'ordinary everyday life', without implying that this representation of 'everyday life' constituted either a 'healthy' or 'unhealthy' lifestyle. The company had also not intended the images to imply the exclusion for any particular group of people. Gilead Sciences denied a breach of Clauses 20.1 or 20.2.

Gilead Sciences stated that it did not intend to pressurise patients or increase the sense of fear and vulnerability that HIV infected patients felt, as alleged. The company appreciated that being diagnosed HIV positive was a very difficult and uncertain time. The advertisement was intended to communicate that the advances seen over the last 10 years in HIV medicine had provided patients with a greater confidence of being able to live their everyday life.

Gilead Sciences took the Code very seriously and remained committed to compliance with it. The company also strongly believed that pharmaceutical companies should retain the right to communicate with the public that they serve, within the guidelines of the Code. The company considered that this communication promoted transparency, accountability and stimulated the better understanding of the valuable research and development work of the pharmaceutical industry in the development of treatments that sought to improve the health of the nation. Gilead Sciences refuted a breach of either Clause 20.1 or 20.2.

PANEL RULING

The Panel noted that the advertisement featured a montage of photographs of people, places and things. The headline 'creating confidence in everyday **life**' was followed by 'HIV treatments have made a huge difference to people's lives, but they can limit the ability to carry on with daily life. To live your life with confidence, Gilead aims to provide products that are convenient and effective'. A strapline in the bottom right hand corner stated 'everyday life'. The advertisement also featured Gilead Sciences' company logo which incorporated the company's US website address (www.gilead.com). The Panel noted that Clause 20.1 of the Code stated that prescription only medicines and certain pharmacy medicines must not be advertised to the general public. Gilead Sciences had placed the advertisement and marketed treatment for those with AIDS. The Panel considered that the advertisement raised awareness of the company's corporate interest in the therapy area. The advertisement might facilitate the market development of Gilead Sciences' products. Nonetheless the Panel did not consider that the advertisement advertised a medicine to the general public. No breach of Clause 20.1 was ruled.

The Panel noted the requirements of Clause 20.2 of the Code that information about medicines which was made available to the general public must be factual

and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their doctors to prescribe a specific medicine. The advertisement included the US website address www.gilead.com which immediately took the reader to a page on a US website which featured three HIV therapies, Truvada, Emtriva and Viread. A fourth product, Hepsera for the treatment of chronic hepatitis C, was also featured.

The advertisement implied that Gilead Sciences provided products which were convenient and effective as opposed to other products which limited a person's ability to carry on with daily life. On balance the Panel considered that the advertisement would encourage HIV patients to ask their doctors to prescribe at least one of the four specific medicines referred to on the website. A breach of Clause 20.2 was ruled. The Panel, however, did not consider that the advertisement raised unfounded hopes of successful treatment such that readers would be encouraged not to adopt a healthy lifestyle. The Panel ruled no breach of Clause 20.2 of the Code in that regard.

During its consideration of this case the Panel noted that the advertisement which was in a UK magazine, designed for a UK audience, referred readers to the company's US website. By referring readers in this way Gilead Sciences had, in effect, brought the US website within the scope of the Code. The Panel requested that this be brought to Gilead Sciences' attention.

Complaint received	**17 October 2005**
Case completed	**29 November 2005**

CASE AUTH/1775/10/05 *NO BREACH OF THE CODE*

GAYS AGAINST GENOCIDE v GLAXOSMITHKLINE

Advertisement in Positive Nation magazine

A gay rights organization, Gays Against Genocide, complained about an advertisement placed by GlaxoSmithKline in Positive Nation magazine. Positive Nation was published monthly and distributed widely throughout the UK by the UK Coalition (UKC) of People Living with HIV and AIDS, a national patient group.

The complainant explained that ten years could elapse between infection with HIV and the need for medication. As there were no set rules about when to start treatment the advertisement was designed to persuade and pressurise people who were HIV positive to ask their doctors for treatment.

The complainant was also concerned that people diagnosed HIV positive must adopt a healthy lifestyle if they were to maintain good health. The advertisement implied that a person's full health was taken care of resulting in those exposed to it not adopting a more healthy lifestyle.

The Panel noted that the advertisement simply stated 'GlaxoSmithKline cares'. A strapline read 'DO UKcare' and incorporated the UKC logo. A statement at the bottom of the advertisement read 'UKC wishes to thank GlaxoSmithKline for their continued support'. There was no reference in the advertisement to medicines or treatments for HIV.

GlaxoSmithKline had placed the advertisement and marketed treatment for those with AIDS. The Panel considered that the advertisement raised awareness of GlaxoSmithKline's corporate interest in the therapy area. The advertisement might facilitate the market development of GlaxoSmithKline's products. Nonetheless the Panel did not consider that the advertisement advertised a particular medicine to the general public. No breach of the Code was ruled.

The Panel did not consider that the advertisement raised unfounded hopes of successful treatment such that readers would be encouraged not to adopt a healthy lifestyle. No breach of the Code was ruled.

A gay rights organization, Gays Against Genocide, complained about an advertisement placed by GlaxoSmithKline UK Limited in the August 2005 edition of Positive Nation magazine. Positive Nation was published monthly by the UK Coalition (UKC) of People Living with HIV and AIDS, a national patient group informing, campaigning, researching and advocating for people with HIV. The magazine was widely distributed throughout the UK to those living with HIV and AIDS.

COMPLAINT

The complainant noted that the time between infection with HIV and the need for medication could be as long as ten years. As there were no set rules by the medical profession about when to start treatment the advertisement was designed to persuade people who were HIV positive to ask their doctors for treatment. The advertisement was clearly meant to pressurise people.

The complainant further noted that people diagnosed HIV positive must adopt a healthy lifestyle if they were to maintain good health. The advertisement implied that a person's full health was taken care of resulting in those exposed to it not adopting a more healthy lifestyle.

The complainant hoped his complaint would lead to a ban on all future advertising in Positive Nation by pharmaceutical companies to people who were HIV positive. Being HIV positive was a vulnerable and fearful time and patients should consult and discuss treatments with their clinicians without this sort of pressure.

RESPONSE

GlaxoSmithKline submitted that its full page advertisement was a corporate advertisement intended to show the company's support for the area of HIV. It comprised the company logo, the headline 'GlaxoSmithKline cares' and at the bottom of the page was the strapline 'DO UKCARE' which incorporated the UKC logo, followed by 'UKC wishes to thank GlaxoSmithKline for their continued support'. The advertisement did not refer to product names, classes of products or to the appropriateness of treatment for HIV infected individuals.

GlaxoSmithKline explained that UKC was an independent patient group with charitable status. Its stated aim was to enable the diverse voices of people living with HIV and AIDS to be heard in order to influence change. As part of GlaxoSmithKline's commitment to educate and empower persons living with HIV and AIDS it was one of a number of patient organisations it supported. This support was in the form of an unrestricted grant from GlaxoSmithKline's Medical Fellowship Fund. GlaxoSmithKline wholeheartedly rejected the allegation that the advertisement in question or its support of the UKC was in any way designed to pressure people in to receiving treatment. The company denied a breach of the Code.

When writing to GlaxoSmithKline to inform it of the complaint the Authority asked it to respond in relation to Clauses 20.1 and 20.2 of the Code.

PANEL RULING

The Panel noted that the advertisement simply stated 'GlaxoSmithKline cares'. A strapline read 'DO UKcare' and incorporated the UKC logo. A statement at the bottom of the advertisement read 'UKC wishes to thank GlaxoSmithKline for their continued support'. There was no reference to medicines or treatments for HIV. The Panel noted that Clause 20.1 of the Code stated that prescription only medicines (POMs) and certain pharmacy medicines must not be advertised to the general public. GlaxoSmithKline had placed the advertisement and marketed treatment for those with AIDS. The Panel considered that the advertisement raised awareness of GlaxoSmithKline's corporate interest in the therapy area. The advertisement might facilitate the market development of GlaxoSmithKline's products. Nonetheless the Panel did not consider that the advertisement advertised a particular medicine to the general public. No breach of Clause 20.1 was ruled.

The Panel noted the requirements of Clause 20.2 of the Code that information about medicines which was made available to the general public must be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. 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 accepted that the advertisement might encourage patients to discuss GlaxoSmithKline's products with their doctor but it did not encourage patients to ask their doctor to prescribe a specific medicine. The Panel did not consider that the advertisement raised unfounded hopes of successful treatment such that readers would be encouraged not to adopt a healthy lifestyle. The Panel ruled no breach of Clause 20.2 of the Code.

Complaint received **19 October 2005**

Case completed **18 November 2005**

CASE AUTH/1777/10/05

ANONYMOUS v SCHERING HEALTH CARE

Invitation to an international symposium

An anonymous complainant alleged that an invitation from Schering to a Betaferon (interferon beta-1b) satellite symposium at the World Congress of Neurology (WCN) meeting in Sydney 2005 was in breach of the Code. The invitation featured a 'Dear Colleagues' letter from the Chairman of the symposium which set out the topics to be covered – these included the results from the BENEFIT study (Betaferon in newly emerging MS for initial treatment).

The Panel noted that the invitation had been sent on the instructions of Schering Health Care Germany without any prior consultation with Schering Health Care in the UK. Nevertheless, as it had been sent to UK health professionals, Schering Health Care UK was responsible under the Code.

The Panel considered that the Chairman's letter promoted Betaferon for early intervention in MS which was not a licensed indication as acknowledged by Schering Health Care. The invitation was misleading with regard to the licensed indications for Betaferon and should have included prescribing information for Betaferon but did not. The Panel considered that the invitation amounted to disguised promotion. Breaches of the Code were ruled.

The Panel noted that the invitation was sent to all health professionals who had pre-registered to attend the WCN. The satellite symposium was to last for an hour and a quarter with three speakers. No further details were given about the satellite symposium and no specific allegations were made by the complainant. The Panel considered that on the evidence before it the arrangements were not inappropriate and no breach of the Code was ruled.

Similarly, on the evidence before it, the Panel did not consider it was unreasonable for Schering Health Care to sponsor delegates to attend the WCN. The sponsorship was not conditional on attending the satellite symposium. The costs paid did not appear to be unreasonable. No breach of the Code was ruled.

Overall the Panel did not consider that high standards had not been maintained; no breach of the Code was ruled. The Panel also did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was used as a sign of particular censure and reserved for such use.

COMPLAINT

An anonymous complainant provided a copy of an invitation from Schering to a Betaferon (interferon beta-1b) satellite symposium at the World Congress of Neurology meeting in Sydney 2005. The invitation featured a 'Dear Colleagues' letter from the Chairman of the symposium which set out the topics to be covered – these included the results from the BENEFIT study (Betaferon in newly emerging MS for initial treatment). The complainant assumed that similar invitations had been sent to others in the UK and alleged that it was in breach of the Code.

When writing to Schering Health Care Ltd the Authority asked it to respond in relation to Clauses 2, 3.2, 4.1, 7.2, 9.1, 10.1 and 19.1 of the Code.

RESPONSE

Schering Health Care explained that prior to receipt of the complaint it had not seen this mailing and did not know that it had been sent to anyone in the UK; the mailing had been distributed in the UK in clear breach of the company's internal procedures and without its knowledge or approval. All company materials used in the UK or with UK health professionals had to be reviewed and approved by Schering Health Care before release, in order to ensure compliance with the Code.

The invitation was developed and sent by an external company on the instructions of Schering Health Care's head office (Schering AG) in Berlin, without any prior consultation with the UK company. It was distributed globally to all health professionals, including 153 UK residents, pre-registered to attend the World Congress of Neurology (WCN), to be held in Sydney from 5-11 November 2005. The company agreed that aspects of the design and content of the invitation were inappropriate, and would therefore not have been approved by Schering Health Care in this form.

The BENEFIT study was a large, multicentre, multinational randomised controlled trial of Betaferon in patients experiencing a first clinical event suggestive of multiple sclerosis. This indication fell outside the current summary of product characteristics (SPC) for Betaferon; an application for a licence extension based on these data was now with the European Medicines Evaluation Agency.

Schering Health Care submitted that, in its opinion, the symposium was balanced and scientific in content and did not contravene the Code. In addition to the BENEFIT data, the symposium gave equal emphasis to presentation of 16-year long-term follow-up data from the original Betaferon pivotal trial in relapsing remitting MS, the patient population of which was consistent with the current licensed indications for the product. The BENEFIT study was included because it represented a major advance in the treatment of MS and was therefore of great scientific interest to neurologists working in this area. BENEFIT was the largest trial to date in patients experiencing a first clinical episode of MS, and was also the only trial to include pre-planned long-term follow-up, in line with current best research practice. Presentation of the results of BENEFIT within a scientific meeting, and discussion of these results with interested clinicians seeking more information, was permitted by the Code (supplementary information to Clause 3) as part of the legitimate exchange of scientific information during

the development of a medicine. Indeed Schering Health Care considered that it had a responsibility to make public the results of its company-sponsored trials at the earliest opportunity. Schering Health Care accepted that the sentence 'The BENEFIT study provides a clear rationale for early intervention in this patient group' was inappropriate when used in an unsolicited mailing and with reference to an unlicensed indication. Also the statement '… Betaferon 250mcg is well accepted by patients', although supported by the BENEFIT data, was inappropriate for the same reasons. Additionally, the company accepted that the invitation should have been amended for UK use to include the prescribing information for Betaferon. However, it contended that otherwise the invitation was not disguised promotion, it did not contain any misleading claims and the symposium itself was not unacceptable. Additionally, in contravention of the company's internal procedures, Schering Health Care had no input into the design of the invitation, was given no opportunity to review, amend or approve it, and was not aware that it had been sent to UK residents. Schering Health Care had taken immediate steps, in conjunction with its head office, to ensure there would be no repetition. Taking these points together, the company denied breaches of Clauses 2, 9.1, 10.1 or 19.1.

Regarding UK delegates to the WCN, Schering Health Care sponsored the travel costs of four UK neurologists for (on average) £4,375 per person, to include registration, travel and hotel costs for the duration of the meeting. All four were experienced consultants and they were therefore of appropriate seniority to gain the most from attending the Congress. The company considered that this amount was justified by the first-class scientific content of the congress as a whole, and that the distance travelled was justified by the prestigious nature of the WCN, which was held only once every 4 years. The WCN was the foremost neurology meeting in the world; previous venues had included London (2001) and Buenos Aires (1997). The WCN offered a unique educational opportunity for UK clinicians, in terms of scientific content and exposure to eminent colleagues and the best clinical practice from around the world. Schering Health Care therefore considered that travel sponsorship for a reasonable number of UK participants was entirely justified in this case, despite the distant location. Sponsorship of four consultant neurologists did not amount to an excessive number of UK delegates for this important meeting, and represented a negligible proportion of the total UK delegation to the WCN. Schering Health Care noted that the travel sponsorship it had provided was for these four UK neurologists to attend the WCN in its entirety, not for them to attend the company-sponsored Betaferon symposium specifically. Indeed, it was entirely possible that they might not attend the symposium and there was certainly no requirement from Schering Health Care that they did so.

PANEL RULING

It was an established principle under the Code that UK companies were responsible for the acts and omissions of their overseas affiliates. The Panel noted that the invitation had been sent on the instructions of Schering Health Care in Berlin without any prior consultation with Schering Health Care in the UK. Nevertheless, as it had been sent to UK health professionals, Schering Health Care UK was responsible under the Code.

The Panel considered that the Chairman's letter promoted Betaferon for early intervention in MS which was not a licensed indication as acknowledged by Schering Health Care. The invitation was thus ruled in breach of Clause 3.2 of the Code. The invitation was misleading with regard to the licensed indications for Betaferon and a breach of Clause 7.2 was thus ruled. The invitation should have included prescribing information for Betaferon but did not; a breach of Clause 4.1 was ruled. The Panel considered that given its rulings above the invitation amounted to disguised promotion and a breach of Clause 10.1 of the Code was ruled.

The Panel noted that the invitation was sent to all health professionals who had pre-registered to attend the WCN. The satellite symposium was to last for an hour and a quarter with three speakers. No further details were given about the arrangements for the satellite symposium and no specific allegations were made by the complainant. The Panel considered that on the evidence before it the arrangements were not inappropriate and no breach of Clause 19.1 of the Code was ruled.

Similarly, on the evidence before it, the Panel did not consider it was unreasonable for Schering Health Care to sponsor delegates to attend the WCN. The sponsorship was not conditional on attending the satellite symposium. The costs paid did not appear to be unreasonable for travel and accommodation given the location of the WCN. Thus the Panel ruled no breach of Clause 19.1 of the Code.

Overall the Panel did not consider that the circumstances were such as to justify a ruling of a breach of Clause 9.1. The Panel also considered that the circumstances did not warrant a ruling of a breach of Clause 2 of the Code which was used as a sign of particular censure and reserved for such use.

Complaint received **24 October 2005**

Case completed **1 December 2005**

CODE OF PRACTICE REVIEW – FEBRUARY 2006

Cases in which a breach of the Code was ruled are indexed in **bold type**.

1652/11/04	**Paragraph 17/Director v Wyeth**	**Switch programme**	**Breach Clause 18.1** **Audit required by ABPI Board** **Re-audit required** **Further audit required in September 2006**	**Appeal by respondent** **Report from Appeal Board to ABPI Board**	**Page 3**
1659/11/04	**Primary Care Trust Medicines Management Support Pharmacist/Director v Wyeth**	**Breach of undertaking**	**Breaches Clauses 2, 9.1, 22** **Audit required by Appeal Board** **Re-audit required in nine months**	**Appeal by respondent** **Report from Panel to Appeal Board**	**Page 10**
1689/3/05	**Servier/Director v GlaxoSmithKline**	**Breach of undertaking**	**Breaches Clauses 2, 9.1 and 22** **Public reprimand by ABPI Board**	**Appeal by respondent** **Report from Panel to Appeal Board** **Report from Appeal Board to ABPI Board**	**Page 15**
1700/4/05	**Paragraph 17/Director v Wyeth**	**Switch programme**	**Breaches Clauses 9.1 and 18.1**	**No appeal**	**Page 20**
1708/5/05	**Brogen Idec v Serono**	**Multiple sclerosis Guidelines**	**Breaches Clauses 2, 3.2, 7.2 and 8.1** **Serono required by ABPI Board to issue a corrective statement**	**Appeal by respondent** **Report from Appeal Board to ABPI Board**	**Page 26**
1717/6/05	**Pfizer v Yamanouchi Pharma**	**Vesicare leavepiece**	**Breaches Clauses 7.2, 7.3 and 7.4**	**Appeal by complainant**	**Page 35**
1731/6/05	**UCB Pharma v Alk-Albelló**	**Promotion of Epipen**	**Two breaches Clause 4.1** **Breach Clause 18.1** **Four breaches Clause 20.1** **Two breaches Clause 20.2** **Two breaches Clause 21.1** **Breach Clause 21.3**	**No appeal**	**Page 45**
1737/7/05	**Anonymous Medical Representative v AstraZeneca**	**Call rates for representatives**	**Breaches Clauses 9.1 and 15.9**	**No appeal**	**Page 52**
1738/7/05	**Bracco UK v GE Healthcare**	**Promotion of Visipaque and Omniscan**	**Two breaches Clause 7.2** **Breach Clause 7.3** **Two breaches Clause 7.8** **Breach Clause 7.10**	**Appeal by respondent**	**Page 56**

1745/7/05	**Anonymous v Abbott**	**Arrangements for meetings**	**Four breaches Clauses 2 and 9.1 Three breaches Clauses 15.2 and 19.1** **Audit required by Appeal Board** **ABPI Board suspended Abbott from ABPI membership for a minimum of 6 months** **Audit required by ABPI Board in May 2006**	**No appeal** **Report from Panel to Appeal Board** **Report from Appeal Board to ABPI Board**	**Page 74**
1753/8/05	**Bristol-Myers Squibb and Otsuka/Director v Lilly**	**Zyprexa leavepiece**	**Breach Clause 7.2**	**No appeal**	**Page 79**
1757/9/05 1759/9/05 & 1760/9/05	**Primary Care Trust Head of Prescribing, a General Practitioner, a Primary Care Trust Director of Public Health and a Practice Support Pharmacist v Servier**	**Coversyl booklet**	**Two breaches Clause 7.2 Breach Clause 7.4**	**No appeal**	**Page 82**
1762/10/05	**Primary Care Trust Clinical Effectiveness Pharmacist v Merck Sharp & Dohme**	**Promotion of Cozaar**	**Five breaches Clause 7.2**	**No appeal**	**Page 88**
1763/10/05	**Primary Care Trust Clinical Effectiveness Pharmacist v Servier**	**Coversyl mailing**	**Three breaches Clause 7.2**	**No appeal**	**Page 92**
1764/10/05	**General Practitioner v Servier**	**Coversyl journal advertisement**	**Breach Clause 7.2**	**No appeal**	**Page 95**
1765/10/05	**General Practitioner v Pfizer**	**Lipitor advertisement**	**Breach Clause 4.1**	**No appeal**	**Page 97**
1768/10/05	**Procter & Gamble v Shire**	**Colazide leavepiece**	**Three breaches Clause 7.2 Four breaches Clause 7.4**	**No appeal**	**Page 98**
1769/10/05	Gays Against Genocide v Gilead Sciences	Material on a website	No breach	No appeal	Page 102
1772/10/05	Gays Against Genocide v Abbott	Advertisement in Positive Nation magazine	No breach	No appeal	Page 104
1773/10/05	Gays Against Genocide v Bristol-Myers Squibb	Advertisement in Positive Nation magazine	No breach	No appeal	Page 105
1774/10/05	**Gays Against Genocide v Gilead Sciences**	**Advertisement in Positive Nation magazine**	**Breach Clause 20.2**	**No appeal**	**Page 107**
1775/10/05	Gays Against Genocide v GlaxoSmithKline	Advertisement in in Positive Nation magazine	No breach	No appeal	Page 109
1777/10/05	**Anonymous v Schering Health Care**	**Invitation to an International Symposium**	**Breaches Clauses 3.2, 4.1, 7.2 and 10.1**	**No appeal**	**Page 111**

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 sixty non member companies have voluntarily agreed to comply with the Code and to accept the jurisdiction of the Authority.

The 2006 edition of the Code covers the advertising of medicines to health professionals and administrative staff and also covers information about prescription only 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, administer, recommend, buy or sell 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
- the provision of information to the general public either directly or indirectly, including by means of the Internet
- 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 William Harbage 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)
By email to: complaints@pmcpa.org.uk.