PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

NUMBER 60 MAY 2008

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.

Annual Report for 2007

The Annual Report of the Prescription Medicines Code of Practice Authority for 2007 has now been published and copies have been sent to all who are on the mailing list for the Code of Practice Review. Further copies are available on request.

There were 127 complaints in 2007 as compared with 134 complaints in 2006. There were 101 complaints in 2005.

The 127 complaints in 2007 gave rise to 122 cases. The number of cases generally differs from the number of complaints, the reason being that some complaints involve more than one respondent company and some complaints do not become cases at all, usually because no *prima facie* case is established.

Of the 295 rulings made by the Code of Practice Panel in 2007, 243 (82%) were accepted by the parties, 40 (14%) were unsuccessfully appealed and 12 (4%) were successfully appealed. This compares with the 6% of rulings which were successfully appealed in 2006.

The Code of Practice Panel met 69 times in 2007 (63 in 2006) and the Code of Practice Appeal Board met 9 times in 2007 (11 in 2006). The Appeal Board considered appeals in 25 cases as compared with 22 in 2006.

The number of complaints made by health professionals in 2007 exceeded the number made by pharmaceutical companies, there being 57 from health professionals and 28 from pharmaceutical companies. This has historically been the usual pattern although in 1996, 1999, 2001, 2002 and 2003 the reverse was true.

The Authority advertises brief details of all cases where companies were ruled in breach of Clause 2 of the Code, were required to issue a corrective statement or were the subject of a public reprimand. These advertisements act as a sanction and highlight what constitutes a serious breach of the Code.

Two advertisements were placed in the BMJ and The Pharmaceutical Journal in 2007 in relation to complaints received during the year and the remainder were published in 2008. Copies of the advertisements are on the PMCPA website.

Updated Code of Practice as agreed by ABPI members

At the Annual General Meeting of The Association of the British Pharmaceutical Industry (ABPI) on 30 April, member companies agreed a revised version of the Code of Practice for the Pharmaceutical Industry. The new Code will come into operation on 1 July 2008 but, during the period 1 July to 31 October, no material or activity will be regarded as being in breach of the Code if it fails to comply with its provisions only because of requirements newly introduced.

There are different transitional arrangements for Clause 4.10 (adverse event reporting) and certain aspects of Clause 23.7 (support of patient organisations). Details are given in the supplementary information to those clauses.

Also agreed was a revised version of the Constitution and Procedure for the Prescription Medicines Code of Practice Authority. This also comes into operation on 1 July but certain aspects will apply only to complaints received on and after 1 July.

Brief details of the main changes are set out below. Full details have been sent to companies and are also available on the PMCPA website (www.pmcpa.org.uk).

It is anticipated that printed copies of the new Code will be available shortly. A copy will be sent to everyone on the mailing list for the Code of Practice Review and bulk orders from companies will be dispatched as soon as possible.

Principal changes to the Code of Practice

General

There has been a reordering of some of the clauses.

Clause 3

Changes are made in relation to the promotion of medicines not licensed in the UK at certain international meetings held in the UK.

Clause 4 and Clause 5

The use of the black triangle symbol is now a requirement of the Code. Obligatory text is required regarding the reporting of adverse events.

Clause 9

Sponsorship declaration must accurately reflect the nature of the company's involvement.

Clause 10 becomes Clause 12

Clause 11 becomes Clause 10

Clause 12 becomes Clause 11

Clause 13 becomes Clause 21

A scientific service for the approval and supervision of non-interventional studies of marketed medicines is now required. The disclosure of details of ongoing clinical trials in line with the Joint Position on the Disclosure of Clinical Trial information becomes a requirement of the Code.

Clause 14

Paper or electronic copies of certificates are now permitted. Final form of the material must still be certified. Certificates for non promotional material must also be kept for 3 years after final use.

Clause 15

New supplementary information is added to require representatives' briefing material to clearly distinguish between expected call rates and expected contact rates for representatives. Targets must be realistic and not such that representatives need to breach the Code to meet them.

Clause 16

Representatives must take the examination within one year of commencing such employment. The Director can allow an extension in certain circumstances.

Clause 17

Samples cannot be used simply as an inducement to prescribe, supply, administer, recommend, buy or sell any medicine. Samples can no longer be provided of any medicine that has been on the UK market for more than ten years.

Clause 18

Non promotional quizzes can be used at promotional meetings to gauge attendees' knowledge; they must be tests of skill with no prizes.

New requirements have been added regarding donations and grants etc to organisations etc that are comprised of

Continued overleaf

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:

Monday, 7 July 2008

Friday, 12 September 2008

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 Nora Alexander for details (020 7747 1443 or email nalexander@pmcpa.org.uk).

How to contact the Authority

Our address is:

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

www.pmcpa.org.uk

Telephone: 020 7747 8880

Facsimile: 020 7747 8881

Copies of the Code of Practice for the Pharmaceutical Industry and of this Review can be obtained from Lisa Matthews (020 7747 8885 or email lmatthews@pmcpa.org.uk).

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.

Principal changes to the Code of Practice continued

health professionals and/or provide healthcare or conduct research and any other type of funding by companies not otherwise covered by the Code.

Clause 19

It has been made clear that extravagant venues are not allowed and companies must not sponsor or organise entertainment such as sporting or leisure events. Meetings for UK health professionals must comply with the Code regardless of whether the meetings are organised by UK company or affiliate and in or outside the UK.

Clause 20 becomes Clause 22

Clause 21 becomes Clause 24

Internet access restriction is not needed if a website that includes open access advertising of prescription only medicines to health professionals also includes information for the public. Each section must be separated and the intended audience identified. Each section must comply with the relevant requirements of the Code.

New Clause 13

Covers non-interventional studies of marketed medicines and includes detailed criteria for prospective non-interventional studies. Publication of summary details and results is strongly encouraged in a manner similar to that for ongoing clinical trials.

New Clause 20

Covers the use of health professionals as consultants to pharmaceutical companies for services such as speaking/chairing meetings, clinical trials, training services, advisory boards etc. Includes detailed provisions such as the need for a written agreement and a strong encouragement to include in the agreement obligations on the health professional to declare the interest when appropriate. Limited market research is excluded.

New Clause 23

The requirements for relationships with patient organisations are now a separate clause. There are more details regarding written agreements. Companies cannot require to be the sole funder of a patient organisation or any of its major programmes. Companies cannot use patient organisation logos or materials without prior written permission. Companies can correct factual errors in patient organisation material but cannot influence text in a manner favourable to their own commercial interests. Companies to make publicly available a list of organisations to which they provide financial support and/or significant indirect/non financial support to include short descriptions of the nature of the support. Sponsorship of all materials/activities must be clearly acknowledged from the outset and the wording must accurately reflect the nature of the involvement.

Clause 22 becomes Clause 25

Principal changes to the Constitution and Procedure

General

More information about the reasons for process, the basis of rulings and inclusion of current practices.

Paragraph 3

Any vacancy for the Chairman to be advertised.

Paragraph 5

The Director to allow similar complaints to proceed if no breach of the Code was ruled by the Code of Practice Panel and no appeal rather than, as currently, those where there was no appeal.

Complainants to be asked about relevant interests when not disclosed in the complaint.

The Chairman to have final view when there is a dispute about inter-company dialogue and the Director's view is not accepted.

Paragraph 6

Previous *prima facie* case determinations removed.

Details regarding criticisms in the media and action to be taken now form Paragraph 6.

Paragraph 7

Made clear that material for appeals must be submitted in writing within the requisite time frame and that new material cannot be introduced at the appeal hearing.

Sets out arrangements for an appeal of a Panel decision that a matter is not subject to the Code.

Paragraph 13

Introduction of the publication of interim case reports for cases which are delayed due to the requirement for a company to undergo an audit.

Advertisement of certain cases now to appear in the nursing press as well as the medical and pharmaceutical press.

Paragraph 17

The ability of the Panel and Appeal Board when considering a case to raise matters not addressed by complainants as complaints has been removed leading to consequential renumbering.

A happy event .....

Etta Logan, the Authority's Secretary, has had a baby boy, Luke Michael, who was born in April. Etta will be on maternity leave until later this year. The Authority sends its best wishes to Etta and her family.

Check the wording of agreements used by third parties

The Authority has received a number of complaints which have arisen from pharmaceutical companies using a third party to email promotional material to health professionals. It is an established principle under the Code that pharmaceutical companies are responsible for work undertaken by third parties on their behalf.

Clause 9.9 of the Code prohibits the use of email for promotional purposes unless with the prior permission of the recipient. Companies are thus reminded that if they use a third party to email promotional material it is essential that they scrutinise the wording of the agreement used to gain permission to send such material. The agreement should form part of the relevant job bag and must be such that health professionals were able to give fully informed consent. The wording must make it abundantly clear that agreement would result in the receipt of promotional emails. Lack of clarity in the wording is likely to lead to a breach of the Code.

PRIMARY CARE TRUST CHIEF PHARMACIST v PFIZER

Champix journal advertisement

The chief pharmacist at a primary care trust queried whether an advertisement for Champix (varenicline) placed by Pfizer in the Health Service Journal (HSJ) was in breach of the Code because the journal was available to those who were not health professionals.

The Panel noted that the HJS was a specialist professional title and described itself as a leading source of news and information on health management and policy.

The Code covered the promotion of medicines to health professionals and appropriate administrative staff. The Code required that material was tailored to the audience to whom it was directed. In the Panel's view it was acceptable for companies to advertise medicines in the HJS provided the advertisement was appropriate for the audience.

The advertisement at issue described, in simple terms, how Champix worked, compared its quit rate with that of another medicine or placebo and referred to its safety and tolerability profile in 4,000 patients. The Panel considered that the content of the advertisement was appropriate for a health professional/NHS management audience. The advertisement was not an advertisement to the public and no breach was ruled.

The chief pharmacist at a primary care trust complained about an advertisement (ref CHA055a) for Champix (varenicline) placed by Pfizer Limited in the Health Service Journal, 11 October 2007.

COMPLAINT

The complainant stated that she was surprised to see an advertisement for Champix in the Health Service Journal (HSJ). As this journal was available to those who were not health professionals, she wondered whether the advertisement breached the Code.

When writing to Pfizer, the Authority asked it to respond in relation to Clauses 12.1 and 20.1 of the Code.

RESPONSE

Pfizer stated that its policy had always been to advertise prescription only medicines (POMs) only in journals that were distributed and read by health professionals and appropriate administrative staff. The main audience for Pfizer's current advertisement included primary and secondary care doctors, nurses, hospital pharmacists, smoking cessation advisers and members of the hospital management and administrative staff responsible for budgeting and resource allocation within NHS trusts.

The HSJ was distributed to members of the health professions and appropriate healthcare management and administrative staff. Additionally, as stated on its website, the journal was 'Targeted at healthcare professionals, it is an integrated online resource and magazine'. Pfizer submitted that the advertisement in the HSJ had not breached either Clause 12.1 or Clause 20.1 and had complied with both the spirit and the letter of the Code.

PANEL RULING

The Panel noted that the HSJ was a specialist professional title which described itself as a leading source of news and information on health management and policy.

The Code covered the promotion of medicines to health professionals and appropriate administrative staff. The Code required that material was tailored to the audience to whom it was directed. In the Panel's view it was acceptable for companies to advertise medicines in the HSJ provided the advertisement was appropriate for the audience.

The advertisement at issue described, in simple terms, how Champix worked, compared its quit rate with that of another medicine or placebo and referred to its safety and tolerability profile in 4,000 patients. The Panel considered that the content of the advertisement was appropriate for a health professional/NHS management audience and thus ruled no breach of Clause 12.1.

The Panel did not accept that the advertisement was an advertisement to the public. The Panel therefore ruled no breach of Clause 20.1.

Complaint received	**16 October 2007**
Case completed	**5 December 2007**

CASE AUTH/2060/10/07

GENERAL PRACTITIONER v TEVA

Guidelines in Practice insert

A general practitioner complained about an insert distributed with the September issue of Guidelines in Practice and entitled 'Making an informed choice. A guide to changing to CFC-free beclometasone inhalers'. The article had been written by a programme director, medicines management, at a primary care trust (PCT). The insert stated on the front cover that it was supported by an unrestricted educational grant from Teva UK Ltd. Prescribing information for Qvar (CFC-free beclometasone dipropionate (BDP)) appeared the inside back page.

The complainant initially thought that the insert was a balanced account of treatment options; that it was 'Supported by an unrestricted educational grant …' and aimed to help health professionals decide which of Qvar and Clenil Modulite (Trinity-Chiesi Ltd's CFC-free BDP) were suitable for patients, supported this view. However, after looking into the supporting evidence in some detail the complainant alleged that the information was not balanced, fair and accurate. The article was potentially misleading and biased.

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

The Panel considered that Teva was inextricably linked to the production of the supplement. There was no arm's length arrangement between the provision of the sponsorship and the generation of the supplement. Teva's agency and the commissioned author produced the article. The company had paid for it to be distributed and in addition it was being used by the representatives for a promotional purpose. Given the company's involvement, and use of it, the Panel considered that the supplement was, in effect, a paid for insert which promoted Qvar.

The complainant noted that favourable plasma cortisol results for Qvar were discussed from just one of three referenced short term studies (Davies *et al* 1998) without discussing the much less favourable results from Gross *et al* 1999.

The Panel noted that Gross *et al* provided data about plasma cortisol levels. At week 12, 96% or more of patients with run in, end of steroid and end of study values had normal cortisol levels. At week 12 the mean percentage change in plasma cortisol from run in was 9.7% (HFA-BDP) 0.1% (CFC-BDP) and 1.9% (HFA-placebo). No clinically meaningful change in clinical chemistry or vital signs were reported in any treatment group at the end of the 12 week treatment period.

The Qvar Summary of Products Characteristics (SPC) (Section 4.4) stated that BDP and its metabolites might exert detectable suppression of adrenal function. Within the dose range 100-800 micrograms daily, clinical studies with Qvar aerosol had demonstrated mean values for adrenal function and responsiveness within the normal range. However, systemic effects of inhaled corticosteroids might occur, particularly at high doses prescribed for prolonged periods. These effects were much less likely to occur than with oral corticosteroids.

There appeared to be an error in Davies *et al*. The abstract at the start of the paper stated that 'Fewer patients on HFA-BDP than on CFC-BDP had plasma cortisol levels below the normal reference range after 12 weeks of therapy (5.1% vs 17.3% respectively)'. These were the figures cited in the insert in question. The results section of Davies *et al*, however, stated that mean plasma cortisol levels were comparable between the two treatment groups at the end of the run-in period, after oral steroid treatment and at the end of the study. However amongst patients with both a run-in and end-of-study plasma cortisol measure more of those treated with CFC-BDP were found to have plasma cortisol levels below the normal reference range and this difference was statistically significant. Readers were referred to a figure which depicted results of just over 5% for HFA-BDP, and just under 15% for CFC-BDP. The figures given in the discussion section of Davies *et al* were 4.35% for HFA-BDP and 14.43% for CFC-BDP. It thus appeared that the figures of 5.1% and 17.3%, as quoted in the abstract, were incorrect.

The Panel considered that in a section headed 'Clinical trial evidence' it was misleading, regardless of the accuracy of the figures cited in the insert from Davies *et al*, to only refer to plasma cortisol data from that study when relevant data had also been published by Gross *et al*. A breach of the Code was ruled.

The complainant noted that emphasis was placed on

a large long-term study (Fireman *et al* 2001) with favourable results for Qvar, however the article failed to mention that it was open labelled. The complainant thought this was important information especially as the short-term studies were randomised, blinded studies.

The Panel noted Teva's submission about the classification of studies as open-label or blinded. The Panel considered that given the amount and nature of other information included about Fireman *et al* it would have been helpful if it had been made clear that this was an open label study. However, on balance the Panel did not consider it was necessarily a breach of the Code not to mention this and ruled no breach.

The complainant noted that the insert discussed the finding of 'higher percentage of symptom-free days' from a long-term study (Price *et al* 2002) without discussing the contrasting results of symptom-free days from Gross *et al*.

The Panel noted that Price *et al* was of a pharmacoeconomic study and queried whether it should be included in a section headed 'Clinical trial evidence'. It also noted a claim regarding comparing symptom-free days from Price *et al* had already been ruled in breach of the Code (Case AUTH/2007/5/07).

The Panel considered that in a section headed 'Clinical trial evidence' it was misleading to omit the Gross *et al* data on symptom-free days. The studies were of different designs, and Gross *et al* included little detail of the symptom-free data but nevertheless stated that 'The number of symptom-free days and nights and β-agonist use were also equivalent in the two active treatment groups' (HFA-BDP and CFC-BDP). A breach of the Code was ruled.

The complainant noted a section of the insert discussed the favourable quality of life results for Qvar (Juniper *et al* 2002). Again, the open labelled design of the study was not stated. Furthermore, less favourable results from Juniper and Buist, (1999) were not discussed.

The Panel noted that the section on quality of life cited Fireman *et al*, Juniper *et al* and Price *et al*.

Juniper *et al* (based on Fireman *et al* data) stated that although the mean improvement in overall quality of life score over 12 months was greater with HFA-BDP (0.34) than with CFC-BDP group (0.10) the difference between the two was less than the minimal important difference of 0.5. This was not mentioned in the article. Juniper *et al* also determined the proportion of patients for whom quality of life had improved, been maintained or deteriorated. There was a greater proportion of patients for whom quality of life had improved and it was this data that was referred to in the insert. A bar chart presented data from Price *et al* based on Fireman *et al*.

Juniper *et al* referred to Juniper and Buist (a twelve week study) which showed a trend to improved quality of life in the HFA-BDP group compared with the CFC-BDP group. It was possible that the benefit was only achieved after long-term therapy. Further studies were needed to explore the time course in greater depth.

The Panel considered that given the title of the article 'Making an informed choice…',it was misleading not to include details of Juniper and Buist in the quality of life section as alleged. Readers would not have appreciated that benefits in terms of quality of life with Qvar might only be achieved after long-term therapy. The Panel ruled a breach of the Code.

The complainant noted that the concluding statement on quality of life was referenced to Juniper *et al* and Juniper and Buist. Juniper and Buist appeared not to support this statement.

The Panel noted that the statement at issue 'There are also data to show improved QoL [quality of life] for patients treated with Qvar over CFC-containing BDP products[28, 37]', was incorrectly referenced. Reference 28 was Juniper *et al* and there was no reference 37 cited. Reference 36 was Juniper and Buist.

The Panel considered its comments about the quality of life data above. It considered that the claim was too general given the data from Juniper and Buist and Juniper *et al*. It thus ruled breaches of the Code.

The complainant alleged that this section implied that a nurse service was provided to a named PCT by Teva. The Code required that services should be referred to in a non-promotional context.

The Panel noted that the the insert referred to an independent service provided by a pharmaceutical company that included nurses who ran extra asthma review sessions. The insert did not link Teva to the service and the service to the PCT was provided by another company in 2000.

In the circumstances the Panel decided there was no breach of the Code.

The complainant noted that the MHRA was specifically mentioned five times in the insert and this might create a perception that the insert was so endorsed.

The Panel did not consider that mention of the MHRA in the insert created the perception that the insert was endorsed by it.

The Panel noted that the Code prohibited reference in promotional material to inter alia the MHRA. The only exemption to this prohibition was if such reference was specifically required by the licensing authority.

The Panel noted Teva's submission that it had been asked by the MHRA to communicate the MHRA guidance that CFC-free BDP should be prescribed by brand name. It did not appear, however that the MHRA had specifically required Teva to refer to the Agency in its promotional material. Even with the agency's acceptance of the use of its name in promotional material, given the wording of the Code it would nonetheless be unacceptable to mention the MHRA in promotional material unless specifically required by the Agency to do so. The Agency's permission or acceptance could not override the requirements of the Code. The Panel therefore ruled a breach of the Code.

A general practitioner complained about an insert (ref HDM/07/047) distributed with the September issue of Guidelines in Practice entitled 'Making an informed choice. A guide to changing to CFC-free beclometasone inhalers' and written by the programme director, medicines management, at a primary care trust (PCT). The insert stated on the front cover that it was supported by an unrestricted educational grant from Teva UK Ltd. Prescribing information for Qvar (CFC-free beclometasone dipropionate (BDP)) appeared on the inside back cover.

General comments

Complainant The complainant stated that initially he thought that the insert was a balanced account of treatment options and the statement 'Supported by an unrestricted educational grant …' together with the stated aims to help health professionals decide which of Qvar and Clenil Modulite (Trinity-Chiesi Ltd's CFC-free BDP) were suitable for patients, supported this view.

He had since looked into the supporting evidence and was concerned that the information provided was not balanced, fair or accurate. He queried what action could be taken to ensure that other colleagues who had received this article were made aware of the potentially misleading and biased content.

When writing to Teva, the Authority initially asked it to respond in relation to Clauses 7.2, 7.4 of the Code and subsequently to Clause 9.5 in addition to Clause 18 cited by the complainant.

Respondent Teva believed that the author had produced a balanced and fair review of the material available. When preparing any scientific manuscript the author had to decide what information to include. The article provided an extensive review of the literature and included 36 references of which 23 were published scientific manuscripts. The topic covered was very large and it was normal practice to refer less to old studies when they had been superseded by newer ones. This practice was followed in this article. The complainant seemed to suggest that older studies somehow invalidated the newer references chosen by the author.

Teva noted that the issues raised were identical to those of previous extensive inter-company dialogue with another company; Teva had already successfully answered these issues.

Teva was also concerned that the complainant seemed not to have read or fully understood the studies he had quoted, as they did not support his views. This was very regrettable and had resulted in an ill informed or misplaced complaint.

Teva believed the article was factually correct, fair and balanced. A statement from the author was provided who stood by its content.

Teva reviewed the items raised by the Authority but as requested it had only referred to items that were covered by Clauses 7.2 and 7.4. If the Panel considered that there were any issues that Teva had failed to address, Teva requested that it was informed accordingly.

Making an informed choice (background)

Market research in 2006 demonstrated that health professionals had a poor understanding of the differences between products containing beclometasone for inhalation with the two different propellant agents: (hydrofluoroalkane (HFA) and chlorofluorocarbon (CFC)) and the issues surrounding their use. This situation had been exacerbated by GlaxoSmithKline's announcement that Becotide/Becloforte would be discontinued by October 2007. Currently there was a recognised lack of direction and advice for PCTs from the Department of Health (DoH).

When large numbers of patients required changes in therapy due to product discontinuations medical education programmes assumed a greater importance. As was standard and commonplace in the pharmaceutical industry, Teva commissioned a communications company to work with a key opinion leader to write an independent article. The aim was to provide PCT decision makers and health professionals with a comprehensive review of the clinical data on the CFC and HFA containing BDP preparations, along with advice on how to manage the transition to CFC-free alternatives.

A Programme Director, Medicines Management, at a PCT agreed to be the author of this article and was engaged by the agency. The agency was paid to complete this project, and the fees paid to the author were negotiated directly between the two parties.

Teva had no part in the creation of the article after agreeing the initial brief. The article was prepared by both the author and the agency. At the outset agreements were put in place and it was clearly stated by Teva that the document would have to go through the Teva approval process for promotional and educational material prior to publication.

At a review meeting to ensure that the content of the article would not contravene the Code, Teva was represented by the brand manager (as project

sponsor), its medical director and its medical information manager. A director of the agency was present as project manager and point of communication to the author. Teva never communicated directly with the author.

Guidelines in Practice was selected to distribute the article based on an evaluation of its readership for appropriateness of audience and a fee was paid. The editor made some minor suggestions for alterations to the article 'Making an informed choice', which were accepted by the author and reviewed by Teva. Final approval was granted on 6 September. Twenty one thousand copies were mailed as a supplement to the Guidelines in Practice, September 2007 edition. A further five thousand copies were supplied to Teva to be used by its field force to provide an independent resource to customers (briefing document provided). The initial feedback from health professionals was that it was well received.

Teva was disappointed that the complainant alleged that the supplement was not balanced, fair and accurate. Teva would demonstrate that this article complied with the Code.

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

The supplement in question had been sponsored by Teva; it had been initiated by the company and Teva commissioned an agency to work with a key opinion leader to create the article. The agency had contacted the author. The article was reviewed by Teva and went through its approval process to ensure compliance with the Code. 21,000 copies were distributed as a supplement to Guidelines in Practice for which Teva had paid a fee; a further 5,000 were supplied to Teva's sales force. The sales force was instructed to use the article proactively in every call where it was appropriate to discuss CFC-free BDP options available to prescribers.

The Panel considered that Teva was inextricably linked to the production of the supplement. There was no arm's length arrangement between the provision of the sponsorship and the generation of the supplement. Teva's agency and the commissioned author produced the article. The company had paid for it to be distributed and in addition it was being used by the representatives for a promotional purpose. Given the company's involvement, and use of it, the Panel considered that the supplement was, in effect, a paid for insert which promoted Qvar. The Panel then went on to consider the allegations as follows.

1 Clinical trial evidence – plasma cortisol

COMPLAINT

The complainant noted that favourable plasma cortisol results for Qvar were discussed from just one of three referenced short term studies (Davies *et al* 1998) without discussing the much less favourable cortisol results from other studies (Gross *et al* 1999).

RESPONSE

Teva stated that the complainant appeared to have misread the insert as it did not state that all three studies measured the plasma cortisol concentration. The three studies [Gross *et al*, Davies *et al*, and Magnussen 2000] were discussed in term of clinical efficacy and then individual studies were reviewed according to the data they presented. These studies were only mentioned briefly as they were old studies and their results had been superseded by the publication of newer studies in much larger groups of patients, which were conducted over a 12 month period and not a short 10-12 week period.

Gross *et al* and Davies *et al* treated patients with oral steroids (30mg prednisolone) for 7-12 days at the beginning of the study period. Despite these shortcomings there were several important facts that should be considered when comparing outcomes.

- Of the three studies, Magnussen did not measure plasma cortisol concentrations so no comment could be made.

- Gross *et al* measured plasma cortisol concentrations at the end of the run-in period, following a short course of oral prednisolone and after randomised inhaled therapy. No data were presented in the manuscript but the authors stated that 'no clinically meaningful changes in clinical chemistry or vital signs were reported in any treatment group at the end of the 12-week treatment period'. In view of this the author of the insert did not include any results as no data were presented in the manuscript and no clinically meaningful changes were reported.

The insert correctly listed results as they appeared in Davies *et al*. Teva noted that in Davies *et al*, high doses of both medicines were used; patients were randomly allocated to receive either Qvar 800mcg/day or CFC-BDP 1500mcg/day.

The way the data was presented was in-line with the Qvar summary of product characteristics (SPC) which stated that 'Within the dose range 100-800 micrograms daily, clinical studies with Qvar have demonstrated mean values for adrenal function and responsiveness within the normal range'.

Teva therefore did not believe that the data regarding plasma cortisol levels was misleading as alleged. It had been presented in a factual and balanced manner. The reason that further data was not included was that the data were not presented in the manuscripts and to state that the results from Gross *et al* study 'were less favorable' was simply untrue, as Gross *et al* stated that there were 'no clinically meaningful differences' between the treatment groups with reference to the biochemical analyses. Also any differences in results presented by Gross *et al* and Davies *et al* were entirely as expected owing to the much higher steroid dose used in Davies *et al*. Teva believed that the contents of the paragraph at issue were correct, balanced and clearly stated, and therefore did not breach Clauses 7.2 and 7.4.

PANEL RULING

The Panel noted that Gross *et al* provided data about plasma cortisol levels. At week 12, 96% or more of patients with run in, end of steroid and end of study values had normal cortisol levels. At week 12 the mean percentage change in plasma cortisol from run in was 9.7% (HFA-BDP) 0.1% (CFC-BDP) and 1.9% (HFA-placebo). Following these results Gross *et al* stated that no clinically meaningful change in clinical chemistry or vital signs were reported in any treatment group at the end of the 12 week treatment period.

The Qvar SPC (Section 4.4) stated that BDP and its metabolites might exert detectable suppression of adrenal function. Within the dose range 100-800 micrograms daily, clinical studies with Qvar aerosol had demonstrated mean values for adrenal function and responsiveness within the normal range. However, systemic effects of inhaled corticosteroids might occur, particularly at high doses prescribed for prolonged periods. These effects were much less likely to occur than with oral corticosteroids.

There appeared to be an error in Davies *et al*. The abstract at the start of the paper stated that 'Fewer patients on HFA-BDP than on CFC-BDP had plasma cortisol levels below the normal reference range after 12 weeks of therapy (5.1% vs 17.3% respectively)'. These were the figures cited in the insert in question. The results section of Davies *et al*, however, stated that mean plasma cortisol levels were comparable between the two treatment groups at the end of the run-in period, after oral steroid treatment and at the end of the study. However amongst patients with both a run-in and end-of-study plasma cortisol measure more of those treated with CFC-BDP were found to have plasma cortisol levels below the normal reference range and this difference was statistically significant. Readers were referred to figure 5 which depicted results of just over 5% for HFA-BDP, and just under 15% for CFC-BDP. The figures given in the discussion section of Davies *et al* were 4.35% for HFA-BDP and 14.43% for CFC-BDP. It thus appeared that the figures of 5.1% and 17.3%, as quoted in the abstract, were incorrect.

The Panel considered that in a section headed 'Clinical trial evidence' it was misleading, regardless of the accuracy of the figures cited in the insert from Davies *et al*, to only refer to plasma cortisol data from that study when relevant data had also been published by Gross *et al*. A breach of Clause 7.2 was ruled.

2 Clinical trial evidence – design of studies

COMPLAINT

The complainant noted that emphasis was placed on a large long-term study (Fireman *et al* 2001) with favourable results for Qvar, however the article failed to mention that it was open labelled. The complainant thought this was important information especially as the short-term studies discussed earlier contrasted in trial design, in that that they were randomised, blinded studies.

RESPONSE

Teva stated that the complainant implied that the way in which Fireman *et al* was not blinded was important but did not clearly state why this was relevant and seemed to relate the data to previous short-term studies that were randomised.

Teva stated that the allegation was misleading as the studies to which the complainant referred were not all blinded. Although Gross *et al* claimed that the study was blinded the authors did not state how this could have been achieved as double-dummy design was not deemed to be appropriate. Gross *et al* stated that 'A desire only to expose patients to one propellant in order to adequately assess the potential for inhalation effects means that a double-dummy design was not feasible'. In the 1990s there was a vogue to call a study 'single blinded' if the patient was not told the medicine they were receiving, which by today's standards would be disregarded unless the medicines were in identical canisters with indistinguishable labelling. An appropriate level of blinding was also unlikely to have been achieved because metered dose inhalers for HFA-BDP and CFC-BDP had different attributes as the products were present in solution and suspension respectively and had different shapes of canisters. Therefore, in the absence of any details extreme caution must be exercised in relation to the claim that Gross *et al* was a blinded study; by today's standards it would be probably classed as an open-label study, as was Fireman *et al* Price *et al* (2002).

Both Gross *et al* and Fireman *et al* made the same statement regarding the use of double-dummy techniques to blind the study and as both groups agreed and published their articles in well-respected peer review journals, it appeared appropriate to follow their lead. This, however, directly conflicted with the complainant's views but as he provided no reasoning Teva could not comment further. One possible explanation for this difference could be that the complainant had not read and analysed the publications appropriately.

In addition, it was now well accepted that when examining patient reported outcomes studies, these should be at least 3-6 months in length, but current consensus was 12 months. The above position was consistent with the European Medicines Evaluation Agency (EMEA) Committee for Medicinal Products for Human Use (January 2006) paper 'Reflection paper on the regulatory guidance for use of health related quality of life (HRQL) measure in the evaluation of medicinal products'. This stated that unless it was a registration study there was no requirement to use double-dummy studies, it was generally regarded as unethical to replace active medication for placebo. According to Fireman *et al*, performing a double-dummy study of 12 months' duration would not be possible due to poor patient compliance over such period and both Fireman *et al* and Gross *et al* agreed that a double-dummy approach would expose patients to additional risk of receiving a second propellant throughout the study without any possible benefit.

Teva believed that the insert included enough information to allow readers to gain a fair and balanced review of the study in question. It was clear that long-term studies post approval were often conducted in an open fashion as it was regarded as unethical to use placebos to permit a double-dummy technique. This would increase the amount of propellant taken by patients and both Gross *et al* (12 week study) and Fireman *et al* (12 month study) agreed with this position.

The apparent concern with taking greater note of old studies would also seem to disregard the current EMEA guidance that patient reported outcomes required studies with a minimum duration of 3-6 months and there was now a tendency to make these 12 months in duration.

Teva therefore submitted that the studies had been correctly described in a manner that did not breach Clauses 7.2 and 7.4.

PANEL RULING

The Panel noted Teva's submission about the classification of studies as open-label or blinded. The Panel considered that given the amount and nature of other information included about Fireman *et al* it would have been helpful if it had been made clear that this was an open label study. However, on balance the Panel did not consider it was necessarily a breach of the Code not to mention this and ruled no breach of Clause 7.2.

3 Clinical trial evidence – symptom free days

COMPLAINT

The complainant noted that the insert discussed the finding of 'higher percentage of symptom-free days' from a long-term study (Price *et al*) without discussing the contrasting results of symptom-free days from Gross *et al*.

RESPONSE

Teva was surprised at this allegation because Gross *et al* and Price *et al* were different studies and simply not comparable. When a clinical study was compared with another it was important to review and compare all of the relevant criteria which for a trial in asthma should include: study selection, objectives, sample size(s), study design and study medication, duration of the study and patient type (inclusion and exclusion criteria). Studies could only be compared if they were comparable in the above evaluations and in this case it was clear that this was not so.

Study selection

In the case of the studies mentioned by the complainant, only two studies had measured symptom-free days; Gross *et al* and Fireman *et al*/Price *et al*. Gross *et al* conducted a small study of 12 weeks' duration and Fireman *et al* presented the efficacy and safety analysis from a 12 month study and Price *et al* presented an analysis of symptom-free days from the same study.

Gross *et al* claimed that there were no differences in symptom-free days between the treatment groups but no supporting data were presented. In the absence of any data indicating symptom-free values and the 95% confidence intervals, this statement must be interpreted with extreme caution. Conversely Fireman *et al*/Price *et al* presented full data on the median values of symptom-free days and the 95% confidence intervals and as the study was conducted over a 12 month period Teva concluded that the conclusions were robust. The differences in favour of the number of symptom-free days experienced by patients receiving HFA-BDP were highly significant (P=0.006). Teva had discussed this matter with Professor Price and he fully supported this conclusion.

Objectives

The objective of Gross *et al* was to confirm if '[due to] improved lung deposition of [Qvar] in comparison to CFC-BDP…lower doses of [Qvar] may be required to provide adequate asthma control'. The primary endpoint variable was 'morning PEF [peak expiratory flow] over week 1 to 3, 4 to 6, 7 to 9 and 10 to 12'. The groups were analysed 'using an analysis of variance ANOVA with treatment, centre and treatment-by-centre interaction terms'. Asthma symptoms were recorded but no data on symptom-free days were presented in the manuscript.

The objective of Fireman *et al* was to 'evaluate the long-term efficacy and safety of switching patients with asthma maintained on stable dose of CFC-BDP pMDI to therapy with HFA-BDP pMDI at approximately half of their previous dose of CFC-BDP'. There was no primary efficacy variable stated in the manuscript but it was stated that PEF (am and pm), FEV1 (Forced Expiratory Volume over 1 second), daily asthma symptoms and number of times beta agonists were used, were recorded.

The objective of Price *et al* was 'To compare the cost effectiveness of hydrofluoroalkane [Qvar] with [CFC-BDP] in patients with chronic stable asthma previously receiving CFC-BDP, from the perspective of a healthcare provider'. The main outcome measure was 'average and incremental cost-effectiveness ratios based upon symptom-free days, improvement in health-related quality of life, and total drug-only direct healthcare costs'.

Sample size

In Gross *et al*, 113, 117 and 117 patients were enrolled into the three treatment groups of HFA-BDP, CFC-BDP and HFA-placebo respectively.

Fireman *et al*/Price *et al* enrolled 473 patients of which 350 received HFA-BDP and 118 received CFC-BDP. Therefore, Fireman *et al*, as it contained a much larger sample size had a significantly greater statistical power than Gross *et al* so it was not surprising that Firemen *et al* detected differences that were not seen in Gross *et al*.

When evaluating a study it was usual practice to consider whether there was an adequate number of patients enrolled to ensure that any conclusion was robust and could withstand scrutiny. In the 1980/90s many studies provided misleading results because insufficient patients were enrolled and later the conclusions might have to be revised or amended following trials in larger numbers of patients. As a result the required sample size was commonly determined from pilot studies, which although too small to provide a reliable conclusion provided an assessment of the likely difference in outcomes that would be encountered in the subsequent study.

Therefore, when considering whether a result was appropriate and robust enough for application to patient care the sample size and the power of the study must be taken into account.

Design and medication

The two studies had very different study designs, and were not directly comparable. It was therefore inappropriate to combine the results and interpret them in the same way as described in the ruling.

Oral steroids modified the symptoms in asthma and this difference alone could make these studies incomparable. Patients in Gross *et al* study all treated with 30mg oral steroids (prednisolone) for 7-12 days demonstrated reversibility of asthma symptoms as assessed by at least 15% increase in morning PEF rate. In a striking contrast, patients in Fireman *et al*/Price *et al* were not allowed any steroids for 30 days before entry into the study. This was a major difference between the two studies and symptoms assessments for such a large oral steroid dose needed to be reviewed with caution.

As oral steroids were very effective in controlling symptoms and generating a feeling of well-being symptom scores could not be regarded as reliable, especially in the first half of the study. Fireman *et al*/Price *et al* on the other hand assessed symptom-free days over a long period of time (12 months) and patients did not receive a large loading dose of oral steroids at the beginning of the study.

Fireman *et al*/Price *et al* and Gross *et al* had very different study durations.

- Gross *et al* had a 10-12 day run-in period followed by 12 weeks' treatment.
- Fireman *et al*/Price *et al* was conducted over 12 months with no oral steroid run-in period.

In Gross *et al* patients were randomised to receive either HFA-BDP at 400mcg/day or CFC-BDP 800mcg/day following the 7-12 days on oral steroid therapy. This medication schedule was biased in favour of the CFC-BDP and the patients had uncontrolled asthma as defined by the fact that the patients had to experience symptoms in the last 5 days of the run-in period. The dose of HFA-BDP was lower than that licensed for use in the UK as indicated by the Qvar SPC which stated that a 2:1 dose ratio of Qvar to CFC-BDP was licensed for use in controlled patients and in patients with uncontrolled asthma the dose of Qvar should be 1:1 compared with CFC-BDP.

This was a major confounding factor in this study design and medication selection. Conversely Fireman *et al*/Price *et al* only admitted patients who had controlled asthma symptoms over the month prior to entry and thus the selection of the dose of 400mcg/day of Qvar was appropriate and in-line with the UK SPC.

Patient type

Another major fundamental difference between these studies was the choice of patients. While the two studies were conducted in patients with asthma, patients in each study differed significantly in degree of the control of symptoms before enrolment. These differences alone might eliminate any short-term therapy benefits.

In Gross *et al* patients had 'at least moderately severe asthma' and 'were required to show signs and symptoms of acute asthma during the last 5 days of run-in [period]'. Gross *et al* defined asthma symptoms as a mean morning PEF between 50% and 80% of predicted normal value plus one of the following: Sleep disturbance on ≥1 nights; asthma symptoms on ≥3 days or use of a beta-agonist inhaler on average twice daily to relieve symptoms.

In Fireman *et al*: 'patients aged ≥12 years with at least 6-month history of asthma (and stable symptoms for the past month) were enrolled'.

The patient populations were therefore not comparable in many ways. This was an important difference between the study populations and there was now general acceptance that studies were required to reflect the real life setting rather than using highly selected patient populations. Herland *et*

al (2005) estimated that if patients were highly selected by the entry criteria as few as 1.3% of patients with asthma would be eligible to enter into the study.

In conclusion Teva submitted that the studies were very different in design and execution and were not comparable. There were major differences in:

- patient types: Gross *et al* studied uncontrolled asthma patients and Fireman *et al*/Price *et al* studied patients with stable symptoms for the last month prior to entry.

- dosing regimens; Gross *et al* used a large prednisolone dose of 30mg/day prior to randomisation of study.

- periods of time: Fireman *et al*/Price *et al* followed patients for 12 months whilst Gross *et al* was only a 12 week study period which was too short to detect meaningful differences in symptom-free days. Only the 12 month study had enough patients and hence power to detect a statistically significant difference in symptom-free days.

In view of these differences between the studies and the fact that the results were accurately presented in the insert Teva did not understand why the complainant was concerned and it submitted that this paragraph did not contravene Clauses 7.2 and 7.4.

PANEL RULING

The Panel noted that Price *et al* was of a pharmacoeconomic study and queried whether it should be included in a section headed 'Clinical trial evidence'. It also noted a claim comparing symptom-free days from Price *et al* had already been ruled in breach of the Code in Case AUTH/2007/5/07.

The Panel considered that in a section headed 'Clinical trial evidence' it was misleading to omit the Gross *et al* data on symptom-free days. The studies were of different designs. It accepted that Gross *et al* included little detail of the symptom-free data but nevertheless stated that 'The number of symptom-free days and nights and β-agonist use were also equivalent in the two active treatment groups' (HFA-BDP and CFC-BDP). The Panel ruled a breach of Clause 7.2.

4 Quality of life

COMPLAINT

The complainant noted that the insert discussed the favourable quality of life results for Qvar (Juniper *et al* 2002). Again, the open labelled design of the study was not stated. Furthermore, less favourable results from Juniper and Buist (1999) were not discussed.

RESPONSE

Teva noted that firstly in the papers cited by the complainant, it was clearly stated that Juniper *et al*, Fireman *et al* and Price *et al*, reported on the dataset from a single study. This was ignored by the complainant. Gross *et al* and Juniper and Buist also reported data from the same study, which was also ignored.

Therefore the first part of the complaint was exactly the same point as raised in Point 3 above. As this question was repeated from the previous paragraph Teva assumed that the complainant had not read the papers in sufficient detail to be aware of the relationship between the studies. Teva therefore referred the question of design and blinding of Gross *et al*, Juniper and Buist vs Juniper *et al*, Fireman *et al* and Price *et al* to its submission in Point 3.

With regard to the second part once again the issue was one of a short-term, underpowered, small study in uncontrolled patients who received oral steroid load compared to a 12 month study in the well controlled patients in a much larger study.

Juniper and Buist was a small study with 113 patients receiving Qvar this was followed by the larger study (Juniper *et al*) with 354 patients receiving Qvar.

Juniper and Buist was described by the complainant as being less favourable than Juniper *et al* which was not the so. The two manuscripts stated:

- Juniper and Buist measured a change in [quality of life] score from baseline and again at the end of the trial, (12 weeks). It was noted that 'The changes in each of the active treatment groups were significantly different from those observed in the placebo group (p 0.003). Although there was a trend in favour of HFA-BDP compared with CFC-BDP, the difference was small and not statistically significant (p=0.29)'.

- Juniper *et al* measured a change from baseline of [quality of life] score at 0, 2, 4, 8 and 12 months. It was noted that 'Improvements from baseline in overall [quality of life] scores were seen for both treatment groups at each time point, but these results were consistently higher for HFA-BDP than CFC-BDP'.

In Juniper *et al* the authors stated 'At month 12, there was a statistically significant difference between treatment groups in change from baseline in overall [quality of life] in favour of HFA-BDP (p= 0.019), which was also seen in the symptom (p=0.041) and emotional function (p=0.025) domains. For the activity limitation domain, the difference between groups at month 12 approached statistical significance (p=0.073)'.

It was therefore noted in both Juniper and Buist (at 3 months) and in Juniper *et al* (at 2 and 4 months) that there was no statistical significance in [quality of life] score change from baseline at these time points. However both trials reported a slightly higher score in favour of HFA-BDP (Qvar) compared to CFC-BDP but the results were highly significant at 12 months.

In conclusion Teva submitted that it was not correct to state that Juniper and Buist demonstrated less favourable results for quality of life when compared to Juniper *et al*. These papers reported consistent results. As the results from Juniper and Buist were consistent with, and superseded by Juniper *et al* which was longer in duration, had a larger sample size and was more recent in publication, the author of the insert did not include the data from Juniper and Buist and Teva agreed with this decision. Notwithstanding the similarity and consistency of results it would also have been inappropriate to combine the studies in the way the complainant suggested as the studies were not comparable in any way as discussed in the previous section.

Teva therefore believed that this section of the insert was well written, fair, factual and not misleading and did not breach either Clause 7.2 or Clause 7.4.

PANEL RULING

The Panel noted that the section on quality of life cited Fireman *et al*, Juniper *et al* and Price *et al*.

Juniper *et al* (based on Fireman *et al* data) stated that although the mean improvement in overall quality of life score over 12 months was greater in the HFA-BDP group (0.34) than in the CFC-BDP group (0.10) the difference between these values (0.24) was less than the minimal important difference of 0.5. This was not mentioned in the article. Juniper *et al* then went on to look at the proportion of patients for whom quality of life had improved, been maintained or deteriorated. There was a greater proportion of patients for whom quality of life had improved and it was this data that was referred to in the insert. A bar chart presented data from Price *et al* based on Fireman *et al*.

Juniper *et al* also mentioned that HFA-BDP patients experienced a significant improvement in the asthma-specific quality of life even when no differences in conventional clinical measurement of lung function was observed. The reason for this difference was not clear. A couple of suggestions were made, these being firstly that HFA-BDP spray was deposited in more peripheral airways and this led to changes in quality of life but were not captured as FEV1 or PEF assessments or secondly the clinical indexes were not sufficiently sensitive to detect changes. Juniper *et al* stated that the lack of correlation was not unexpected as it was a well documented finding which highlighted the need to assess asthma-specific quality of life in clinical trials.

Juniper *et al* referred to Juniper and Buist which showed a trend to improved quality of life in the HFA-BDP group compared with the CFC-BDP group. It was possible that the benefit was only achieved after long-term therapy. Further studies were needed to explore the time course in greater depth.

Juniper and Buist was based on Gross *et al* and concluded that HFA-BDP was as effective as CFC-BDP in sustaining improvements in quality of life following withdrawal of 7 to 12 days of prednisolone. The study lasted 12 weeks and stated that the number needed to treat with HFA-BDP in order for one patient to benefit compared to CFC-BDP treatment was 21.1. (The figure in Juniper *et al* and mentioned in the insert was between 7 and 8.)

The Panel considered that given the title of the article 'Making an informed choice…', it was misleading not to include details of Juniper and Buist in the quality of life section as alleged. Readers would not have appreciated that benefits in terms of quality of life with Qvar might only be achieved after long-term therapy. The Panel ruled a breach of Clause 7.2.

5 Conclusion

COMPLAINT

The complainant noted that the concluding statement on quality of life was referenced to Juniper *et al* and Juniper and Buist. Juniper and Buist appeared not to support this statement.

RESPONSE

Teva submitted that the complainant simply re-iterated the text in Point 4 and this was fully answered.

PANEL RULING

The Panel noted that the statement at issue 'There are also data to show improved QoL [quality of life] for patients treated with Qvar over CFC-containing BDP products[28, 37]', was incorrectly referenced. Reference 28 was Juniper *et al* and there was no reference 37 cited. Reference 36 was Juniper and Buist.

The Panel considered its comments about the quality of life data above. It considered that the claim was too general given the data from Juniper and Buist and Juniper *et al*. It thus ruled breaches of Clauses 7.2 and 7.4.

6 Extra clinics

COMPLAINT

The complainant alleged that the insert implied that a nurse service was provided to a named PCT by Teva.

Clause 18 clearly stated that services should be referred to in a non-promotional context.

RESPONSE

Teva stated that a nurse service was provided to the named PCT in 2000. It was not sponsored by Teva UK Ltd or Ivax. The complainant was incorrect. The insert clearly stated that the nurse service was provided by 'a pharmaceutical company' and not Teva as stated by the complainant.

The provision of this nurse service pre-dated the

acquisition of Qvar by Ivax by several years. Therefore, any complaint should be directed to the company which was the marketing authorization holder at the time. Teva stated that it could not comment further.

PANEL RULING

The Panel noted that the complainant was correct in that the provision of medical and educational goods and services should not be linked to the promotion of a medicine.

The insert referred to an independent service provided by a pharmaceutical company that included nurses who ran extra asthma review sessions. The insert did not link Teva to the service and the service to the named PCT was provided by another company in 2000.

In the circumstances the Panel decided there was no breach of Clause 18.4.

7 Reference to the Medicines and Healthcare products Regulatory Agency (MHRA)

COMPLAINT

The complainant noted that the MHRA was specifically mentioned five times in the insert and this might create a perception that the insert was endorsed by the UK authority.

RESPONSE

Teva refuted this suggestion totally as it was very clear that the statements at issue only related to the MHRA guidance about the prescription of CFC-free BDP by brand. The insert had cited this guidance because, as stated by the MHRA, incorrect prescribing of CFC-free BDP was a major issue relating to patient safety. It was also essential to indicate that this was not a company warning or guideline, which could often be ignored, but instead was an alert from the MHRA which should be followed. If Teva was to make these statements it believed health professionals could ignore the warnings and thus put patient safety at risk. Teva had had several discussions with both the MHRA and DoH which culminated in the MHRA guidance in August 2006. It had been informed that it was appropriate for Teva to communicate this message to health professionals. This was further reinforced to the Teva staff at a meeting on 1 August 2007 attended by the DoH and the MHRA. However in view of the large numbers of complaints Teva had recently received via the Authority it now submitted each item where the guidance was mentioned to the MHRA for approval and in future each item would be appropriately approved.

Teva believed that it was appropriate to ensure that health professionals prescribed CFC-free BDP by brand as recommended by the MHRA and would include these recommendations in all communications.

As this was agreed with the MHRA Teva did not believe that this contravened Clause 9.5 but to ensure that there was no ambiguity it would continue to obtain MHRA approval each time it mentioned and referenced the MHRA guidance.

PANEL RULING

The Panel did not consider that mention of the MHRA in the insert created the perception that the insert was endorsed by it.

The Panel noted that Clause 9.5 prohibited reference in promotional material to inter alia the MHRA. The only exemption to this prohibition was if such reference was specifically required by the licensing authority.

The Panel noted Teva's submission that it had been asked by the MHRA to communicate the MHRA guidance that CFC-free BDP should be prescribed by brand name. It did not appear, however that the MHRA had specifically required Teva to refer to the agency in its promotional material. Even with the agency's acceptance of the use of its name in promotional material, given the wording of Clause 9.5 it would nonetheless be unacceptable to mention the MHRA in promotional material unless specifically required by the agency to do so. The agency's permission or acceptance could not override the requirements of the Code. The Panel therefore ruled a breach of Clause 9.5.

During its consideration of this point the Panel noted that Teva had provided a copy of email correspondence between its agency and the MHRA wherein the MHRA consented to use of its name in a piece of promotional material. The matter had been discussed with the MHRA Director of Communications. The Panel was concerned that there did not appear to be communication with the post-licensing division of the MHRA.

Complaint received	**18 October 2007**
Case completed	**28 January 2008**

CASE AUTH/2065/11/07 and AUTH/2066/11/07

ANONYMOUS REPRESENTATIVES v TEVA

Representative call rates

Two anonymous Teva representatives (non-contactable) complained separately about their call rates.

The complainant in Case AUTH/2065/11/07 stated that since early 2007 senior managers had set excessive activity targets for calls made on GPs, practice nurses, and hospital doctors. Managers went out of their way to tell representatives to comply with the Code but in reality the only way that the targets could be achieved and sustained was by breaching the Code. Most representatives could not achieve these activity rates so in quarter three 2007 the payment of bonuses was linked to activity rates and to having at least 30 appointments in the diary over the following four months.

The representative explained that his ability to achieve target call rates was not helped by having several surgeries on his territory which did not see representatives and others which would only grant one appointment a year. Despite doing everything possible to get appointments the complainant calculated that in order to get his bonus in Quarter 4 he would have to see more than six GPs every day.

The complainant in Case AUTH/2066/11/07 alleged that there was undue pressure placed upon representatives to achieve unfair and unjust call rates. The latest bonus payments were linked to the achievement of certain call rates and the numbers of appointments in diaries. Failure to achieve specific numbers led to non payment of bonus and the fact that dozens of representatives did not receive any payment suggested that this was an unfair scheme. The complainant was concerned that, through this ill thought through scheme, representatives were being indirectly pressurised to breach the Code.

The Panel noted that supplementary information to the Code stated that the number of calls made on a doctor or other prescriber by a representative each year should normally not exceed three on average excluding attendance at group meetings and the like, a visit requested by the doctor or other prescriber or a visit to follow up a report of an adverse reaction. Thus although a representative might speculatively call upon or proactively make an appointment to see a doctor or other prescriber three times in a year, the number of contacts with that health professional in the year might be more than that. In the Panel's view briefing material should clearly distinguish between expected call rates and expected contact rates.

The Panel noted Teva's submission that its representatives were very clear about the definition of contact rate. The Respiratory mandate and the Teva Brands mandate stated that 'There should not be more than 3 unsolicited calls in any one year on any one individual customers [sic]'. Various reference points were given including to Clauses 15 and 19 of the Code. However it did not appear that the representatives were provided with the definitions of 'contact rate' and 'call rate'. Further it appeared that Teva was confused about the difference. Graphs entitled 'Area example – call frequency' were each headed call frequency whereas Teva's submission referred to them as showing 'contact rate'. The graphs showed that some customers were being called upon more than 3 times per year. The requirements of the Code related to the individual representative and thus if one representative made 2 calls on a doctor it did not mean that another representative could make 4 calls upon another. Similarly if a representative only called once upon one doctor, he could not call five times upon another.

The Panel noted Teva's original submission that '… Teva at a local level … was not breaching the Code in terms of exceeding three unsolicited calls *on average* in one year' (emphasis added). The Panel was uncertain whether Teva had taken account of the fact that the supplementary information to the Code referred to the number of calls on doctors or other prescribers. It appeared that the representatives might be calling on health professionals who were not prescribers and these would not be subject to the restrictions in the supplementary information.

The Panel noted that it had not been provided with clear information about the frequency of contact expected on individual health professionals. There did not appear to be any information about the number of contacts per customer per year. The Panel accepted fully that it was for a company to decide upon its call rates and contact rates provided they complied with the Code. The Panel did not consider that it was necessarily a breach of the Code for Teva to require its representatives to have 30 booked appointments.

The Panel considered that taking all the circumstances into account the representatives' instructions did not sufficiently explain the differences between call rates and contact rates. In the context of Teva's concern that the data was below Teva's expectations and activity target, the Panel considered that without further explanation the briefing documentation together with the company's submission advocated a course of action which was likely to breach the Code. A breach of the Code was ruled.

The Panel considered that the activity graphs were confusing but on balance decided that these did not provide evidence that over calling had occurred and thus no breach of the Code was ruled in that regard.

Two anonymous Teva UK Ltd representatives (non-contactable) separately complained about representative call rates.

Case AUTH/2065/11/07

COMPLAINT

The complainant stated that since early 2007 senior managers had set excessive activity targets for representatives. These activity targets related to calls made on GPs, practice nurses, and hospital doctors and even though they went out of their way to tell representatives that they must comply with the Code in relation to activity, the reality of the situation was that the only way that these rates could be achieved and sustained was by breaching the Code. This they knew! Most representatives could not achieve these activity rates so part way through quarter three 2007 they linked the payment of bonuses to activity rates and to having at least 30 appointments in the representative's diary over the following four months.

On the complainant's territory, like many others, there were several surgeries on the target list which stated that they did not wish to see medical representatives and that they must not visit them again. The complainant's performance was still judged against the activity on these surgeries and the fact that they did not see representatives meant that he needed to make more calls on other customers to make up his overall rates. Many surgeries only gave one appointment for each representative per year. The complainant had to respect this yet the senior managers expected him to see these customers more than once by holding a meeting and then going back to see what they thought of the meeting was etc. He had done everything he could to get appointments with GPs, nurses, practice managers and others at every surgery on his list and still he could not get enough to get his bonus. Some people were now lying to say they had appointments that they did not really have, just to get their bonuses. He did not have more than thirty appointments which meant that he would never achieve his sales bonuses. To make things worse Teva said that representatives could get their bonus in Quarter 4 if they were able to make up the shortfall. The complainant would need to see more than six GPs every day to make up the shortfall.

At the last Teva conference the medical director referred to a complaint that had been made to the ABPI about people being pressurised to get upgrades (Enhanced Asthma Care Service [Case AUTH/2017/7/07]). He said that there had never been any pressure and this was backed up by the brands director. The representatives were all amazed about this – some people were sacked for not getting these upgrades! The representatives were all made to feel uncomfortable and it was obvious that complaining to the ABPI was something that they Teva was very unhappy about.

Case AUTH/2066/11/07

COMPLAINT

The complainant stated that he was concerned that there was undue pressure placed upon representatives to achieve unfair and unjust call rates. The latest bonus payments were linked to the achievement of certain call rates and the number of appointments in diaries. Failure to achieve specific numbers led to non payment of bonus and the fact that dozens of representatives did not receive any payment suggested that this was an unfair scheme. The complainant was concerned that, through this ill thought through scheme, representatives were being indirectly pressurised to breach the Code.

When writing to Teva, the Authority asked it to respond in each case in relation to Clauses 2, 9.1, 15.4 and 15.9 of the Code.

Cases AUTH/2065/11/07 and AUTH/2066/11/07

RESPONSE

Teva was surprised that the complainants had chosen this particular route to express their concerns as Teva would consider this to be a line management discussion in the first instance. Teva assumed that these anonymous complainants had used this 'anonymous' route, intentionally bypassing the internal processes, because they knew that their managers would have all the details regarding their individual performance over the year and how this compared to company and industry wide performance. Their line manager therefore would be able to put their concerns in context based on fact and not misleading hearsay or on one sided personal opinions of what was a fair expectation.

With regard to the suggested increasing pressure in relation to daily roles and expectations, Teva provided key performance indicators in order that an individual's expectations and performance could be assessed in a clearly defined framework. In addition Teva had implemented company wide management processes to help support all staff to help ensure standards and targets in all departments could be achieved.

Teva had an 'open door' policy to UK senior managers and had a detailed internal complaints procedure which helped and supported employees to tell management (outside of the UK if desired) about any activities and behaviours they considered to be unethical, this process was non-judgemental and anonymous. All field-based staff received training on this in Quarter 3, 2007. Amongst other things it covered a course of conduct which seemed improper for behaviour in Teva or which might compromise or embarrass the individual or Teva, if it were known by co-workers or the public.

Excessive activity targets

Virtually all employees within the pharmaceutical

industry were set targets on a number of parameters. Contact rates for sales teams were accepted as an industry norm.

National core contact rate calculation (definition: contact rate was a face to face meeting via either a booked appointment or a requested call in response to an enquiry by a health professional, or a contact made at a meeting):

On average a Teva representative had a customer base of 1,200 and hence appropriate focus was placed on planning for representatives, this included booking appointments.

Teva believed the contact rates set were appropriate given the customer base and were in line with those of other pharmaceutical companies.

Clause 15.4 suggested that representatives should not normally exceed three unsolicited calls on average in one year. This did not include attendance at meetings and the like or those requested by the health professional in response to a specific enquiry. The team mandate clearly recognized this and referenced the appropriate section of the Code.

Teva provided a coverage and frequency report for an average Teva region consisting of nine representatives and stated that it clearly demonstrated that Teva on a local level (and if extrapolated up to a national level) was not breaching the Code in terms of exceeding three unsolicited calls on average in one year.

Given the above, Teva did not believe that this was in breach of Clauses 9.1, 15.4 or 15.9.

Forward planning – 30 appointments in a representative's diary

Planning and organisation was a core competency for representatives, having a well-planned diary was part of that competency. Like most organisations appraisals were based on clearly defined competencies with expectations and targets set around them.

Teva did not know why the complainants believed that having 30 forward booked appointments was unrealistic. Thirty appointments represented on average less than 0.025% (average customer base 1,200/30 appointments) of their customer base. [In response to a request from the Panel Teva subsequently corrected the 0.025% to 2.5% and apologised for its initial error.] Teva noted that this objective of 30 appointments was based on all customer groups not just GPs. Teva firmly believed that in setting these objectives it had acted in the spirit of the Code and ensured that its representatives based their contact with health professionals via pre-arranged appointments (in line with the Code) and therefore did not inconvenience health professionals with unsolicited calls. This information was communicated to the sales force appropriately.

Given the above Teva did not believe that this was in breach of Clauses 9.1, 15.4 or 15.9.

Quarter 4 incentive payments

Teva noted that its representatives were paid a fixed basic salary that formed the majority of their remuneration package, the incentive scheme did not form part of their employment contract and was awarded entirely at the discretion of Teva. For the avoidance of doubt, the scheme could be amended or withdrawn at any time, and without notice, by Teva. This was all clearly set out in the Terms & Conditions of the scheme.

It was not unreasonable to expect that any targets set in any given year were tracked against performance for all employees within Teva. The sales force was no exception to this. It was not unreasonable to set an appropriate incentive based on achievement of any set of performance indicators.

The Teva Incentive Scheme rewarded and recognized highly performing representatives against some key core competencies of the role;

- appropriate calling on customers within the remit of the Code;
- appropriate planning to ensure optimal productivity.

Teva set standards and objectives at all levels that it monitored on an ongoing basis, national contact rate was one such objective. Throughout the year the Teva brands team had been below the industry average.

In July 2007 achievement of key performance indicators was linked to achievement of sales target to recognise that the sales targets were based on figures that assumed a CFC phase-out early in 2007, various factors in the market meant this had not happened as quickly as predicted. Sales targets were reduced by 15% on average in recognition that the targets were stretching in this dynamic environment.

Teva believed in giving representatives every opportunity to meet or exceed their clearly defined targets and so a 'catch-up' facility was put in place to give all representatives a fair and equal chance of achieving their annual performance measures. The Quarter 4 catch-up was designed to allow those top-performing representatives who were close to achieving their performance measures a further opportunity to meet them. It was also accepted in the industry that Quarter 3 contact rates were lower than any other quarter of the year due to the holiday season and national sales meetings traditionally happened in September. Therefore by instigating the Quarter 4 catch-up Teva had tried to help representatives achieve their targets.

The incentive scheme as laid out in the Terms & Conditions was paid upon a representative achieving only 75% of the core contact rate of their total customer population and at least 100% of their sales target. The key performance indicators helped maintain a clearly defined framework for measurement of performance and incentive payment as laid out clearly in the Representative Mandate.

Sales force incentives were inextricably linked to day-to-day job performance and achievement of sales targets; poor performance in any profession was seldom rewarded and was therefore often the source of disgruntlement and resentment to management. The poor performance was often justified by individuals externalizing the issues and blaming it on factors that were 'not their fault' or just plain unfair.

Teva was very disappointed that actions designed to help representatives achieve their targets had been misrepresented as undue pressure by an alleged current employee to justify their own poor performance and consequent lack of bonus payment. One complainant stated they would need to see six GPs every day in Quarter 4 to make up the shortfall; this suggested poor performance. The incentive payment was linked to, inter alia, a contact rate of 2.7 a day. In saying that they would have to see six GPs a day, Teva concluded that in the preceding quarter they had seen virtually no customers at all and/or they did not understand how the incentive scheme worked, which if they had gone to their line manager could have been clarified. Unfortunately as this alleged current employee had complained anonymously, Teva could only speculate as to why they had avoided positive communication with their line manager. This representative seemed to have included this figure of six GPs a day more for its shock value than relevance as the contact rate was on all customers not just GPs.

Given the above information Teva did not believe that this was in breach of Clauses 9.1, 15.4 or 15.9.

Sales conference

As required by the Code any ruling against a company should be communicated to its employees. The presentation was deemed to be important and serious and delivered appropriately due to the company having been ruled as having breached numerous clauses, including Clause 2. Teva had subsequently appealed against this ruling.

Teva did not believe that the current case was a breach of Clauses 9.1, 15.4 or 15.9.

Teva strongly denied that 'people were sacked' for not getting upgrades; Teva assumed this was used to make the complaint more shocking and alarmist and like the rest of the complaint it was based on spurious and intentionally misleading information.

Teva firmly believed that it had acted within the spirit of the Code and defended its right to manage its business responsibly under its own corporate governance guidelines and did not believe it had breached any of the clauses cited.

FURTHER RESPONSE FROM TEVA

In response to a request for further information Teva submitted that the Teva Brands Mandate and the Respiratory Mandate related to the contact rates for promotion of respiratory products. The two sales teams both promoted the same range of products. Teva had not defined the difference between contact rates and call rates per se in the respiratory document but clear reference was made to, inter alia, the Code in both team mandates. The reference to the Code clearly explained the difference and why this was important specifically in relation to the number of unsolicited calls per year to an individual health professional. Teva submitted that its earlier response clearly stated the definition of contact rate as follows and this was clearly understood by sales force and sales force management:

> '**National core contact rate calculation** (definition: contact rate is a face to face meeting via either a booked appointment or a requested call in response to an enquiry by a healthcare professional, or a contact made at a pre-arranged meeting)'.

Regular training sessions were run for both sales teams that updated and refreshed knowledge on the Code and specifically the requirements of Clause 15.

With regard to the local data Teva provided further information as to why this demonstrated there was no breach of the Code with regard to not exceeding 3 unsolicited calls per year. The analysis with regard to all customers showed that for this particular geographical area this sales team (9 representatives) year to date had seen approximately 2,300 individual different customers once. Of these approximately 750 had been seen twice. Of the 750 customers seen twice, a further 350 (approximately) had been seen three times, and so on. The series of graphs was based on contact rate not call rate. Additional graphs broken down by customer groups were also provided.

Therefore, what this series of graphs demonstrated was that at a typical individual area level Teva was not 'overcalling' as representatives only saw the majority of customers once. This was an indicative picture across the other area sales teams.

The figures were below Teva's expectations and activity targets: therefore Teva deemed it appropriate to link activity to bonus to drive the right planning and organisation behaviours in the sales force. Teva did not believe this to be unreasonable based on the under performance being delivered against core performance indicators that had been set.

Teva stated that the phrase '75% of core contacts' meant an achievement of 75% of their individual core contact rate on the key customer group. Core contacts for Teva Brand were GPs, practice nurses, and hospital doctors. On average each Teva Brands representative had a customer base of approximately 1,200. No two territories were identical in terms of customer number or access to health professionals and so Teva had varied the targets to best reflect the local environment.

Teva Respiratory representatives did not see secondary care customers, therefore their customer

average was approximately 1,100 per territory.

Teva did not believe that the activity targets set were excessive considering the number of core targets customers a representative had and the industry benchmarking data in comparison to the Teva performance.

Teva assumed that 25% of health professionals would not see representatives; this was factored into the contact rate objectives.

The 30 appointment objective was based on all customer groups. If a representative only had appointments booked with one group of health professionals, eg nurses, the line manager would seek to understand why this was the case and develop a training needs analysis to help the representative focus more appropriately.

PANEL RULING

The Panel noted that the supplementary information to Clause 15.4 stated that the number of calls made on a doctor or other prescriber by a representative each year should normally not exceed three on average excluding attendance at group meetings and the like, a visit requested by the doctor or other prescriber or a visit to follow up a report of an adverse reaction. Thus although a representative might speculatively call upon or proactively make an appointment to see a doctor or other prescriber three times in a year, the number of contacts with that health professional in the year might be more than that. In the Panel's view briefing material should clearly distinguish between expected call rates and expected contact rates.

The Panel examined all the documents. It noted Teva's submission that its representatives were very clear about the definition of contact rate. The Respiratory mandate and the Teva Brands mandate stated that 'There should not be more than 3 unsolicited calls in any one year on any one individual customers [sic]'. Various reference points were given including to Clauses 15 and 19 of the Code. However it did not appear that the representatives were provided with the definitions of 'contact rate' and 'call rate'. Further it appeared that Teva was confused about the difference. The set of graphs entitled 'Area example – call frequency' were each headed call frequency whereas Teva's submission referred to the graphs as showing 'contact rate'. The Panel disagreed with Teva's submission that these graphs demonstrated that at a typical individual area level Teva was not over calling on customers as the majority were only being seen once by representatives. The graphs clearly showed that some customers were being called upon more than 3 times per year. The requirements of the Code related to the individual representative and thus if one representative made 2 calls on a doctor it did not mean that another representative could make 4 calls upon another. Similarly if a representative only called once upon one doctor, he could not call five times upon another.

In this regard the Panel noted Teva's original submission that '… Teva at a local level … was not breaching the Code in terms of exceeding three unsolicited calls **on average** in one year' (emphasis added). The Panel was uncertain whether Teva had taken account of the fact that the supplementary information to Clause 15.4 referred to the number of calls on doctors or other prescribers. It appeared that the representatives might be calling on health professionals who were not prescribers and these would not be subject to the restrictions in the supplementary information to Clause 15.4.

The Panel noted Teva's submission that it 'ensured that its representatives based their contact with health professionals via pre-arranged appointments (in line with the Code) and therefore did not inconvenience health professionals with unsolicited calls'. It was not a requirement of the Code that doctors should only be seen via pre-arranged appointments, representatives could, if they wished, speculatively 'cold-call' upon health professionals. Whether a representative called upon a doctor via a 'cold-call' or through a one-to-one appointment arranged by the representative (as opposed to one requested by the doctor or to follow-up on an adverse reaction) both types of visit would constitute an unsolicited call, of which no more than three should be made by any one representative to any one doctor or other prescriber in a year.

The Panel noted that it had not been provided with clear information about the frequency of contact expected on individual health professionals. It noted from the mandates that representatives were expected on average to contact either 6.95 or 5.4 customers per day. Again there appeared to be an inconsistency between Teva's submission and the supporting documentation. Teva stated that the incentive payment was linked to a rate of 2.7 a day. Teva also referred to a Quarter 4 catch up and that sales targets were reduced by 15% on average. This appeared to be inconsistent with the mandates which gave the GP contact rates as 3.4 per day or 3.6 per day.

There did not appear to be any information about the number of contacts per customer per year. From the graphs setting out the activity reports, the Teva objective for GPs appeared to be just over 3.5 per quarter for Quarters 1, 2 and 3. This appeared to be per month for October and November. This could be read as a representative having to contact one doctor 3.5 times for Q1, 3.5 times Q2 and 3.5 times Q3, and either 3.5 times per month October, November, December, or 3.5 times in Q4. Giving a total of either 14 or 21 per year. The industry average appeared to be 2 and the industry maximum appeared to be just over 2. The Panel accepted fully that it was for a company to decide upon its call rates and contact rates provided they complied with the Code. The Panel did not consider that it was necessarily a breach of the Code for Teva to require its representatives to have 30 booked appointments.

The Panel considered that taking all the circumstances into account the instructions to representatives were not sufficiently clear about the differences between call rates and contact rates noting in this regard the mandate documents. In the context of Teva's concern that the data was below Teva's expectations and activity target, the Panel considered that without further explanation the briefing documentation together with the company's submission advocated a course of action which was likely to breach the Code. A breach of Clause 15.9 was ruled.

The Panel considered that the graphs were confusing as noted above but on balance decided that these did not provide evidence that over calling had occurred and thus no breach of Clause 15.4 was ruled.

The Panel did not consider the circumstances warranted a ruling of a breach of Clauses 2 or 9.1.

Complaints received

AUTH/2065/11/07	**15 November 2007**
AUTH/2066/11/07	**16 November 2007**
Cases completed	**11 February 2008**

CASE AUTH/2071/11/07

GENERAL PRACTITIONER v TAKEDA

Competact and Actos leavepiece

A general pracationer complained that in a leavepiece for Competact (pioglitazone and metformin) and Actos (pioglitazone) issued by Takeda, data from Lincoff *et al* (2007), a meta-analysis to evaluate the effect of pioglitazone on ischaemic cardiovascular events, was presented in a misleading way. The advantages of pioglitazone were presented in relative risk while the disadvantages were given in terms of absolute risk. If the absolute risk was portrayed as a relative risk then pioglitazone had an increase in serious heart failure of 25-30%.

The Panel noted that the leavepiece contained, *inter alia*, two claims '18% relative risk reduction seen with pioglitazone treatment in the composite primary outcome of mortality, MI or stroke compared to the control group' and further down the page 'The meta–analysis showed an increase in serious heart failure with pioglitazone (2.3% vs 1.8%), but there was no corresponding increase in mortality' both of which were referenced to Lincoff *et al*.

The Panel considered that the presentation of the data in the leavepiece was misleading. To provide one aspect of the information as a reduction in relative risk and another, the risk of serious heart failure, only as an increase in absolute risk was misleading as alleged. It was not made clear that the serious heart failure date represented an absolute risk. A breach of the Code was ruled.

Upon appeal by Takeda the Appeal Board noted the company's submission regarding the way in which risks were conventionally reported in scientific papers, summaries of product characteristics (SPCs) and the like. The leavepiece at issue, however, was a promotional item which thus had to meet the requirements of the Code. The leavepiece had, in effect, condensed the main findings of Lincoff *et al* to one sheet of A4 and in that regard it lacked the additional information which would have otherwise provided a context for the figures reported.

The Appeal Board noted that in the abstract of Lincoff *et al*, the data synthesis section detailed the statistical outcome of the study. The primary composite outcome of death, MI or stroke was reported in terms of absolute risk (4.4% for pioglitazone vs 5.7% for control) with a hazard ratio of 0.82 which had been translated into the leavepiece as an 18% relative risk reduction. The same set of figures was reported for the increased risk of serious heart failure (2.3% for pioglitazone vs 1.8% for control) only in this case the hazard ratio of 1.41 had not been translated into the leavepiece as a 41% relative increased risk. Thus, although the same set of data was reported for the two outcomes they had been reported differently in the leavepiece.

The Appeal Board noted that health professionals knowing only the relative risk of an event or events happening, without also knowing the absolute risks involved, would be unable to judge the clinical impact of the information presented; with regard to the two claims at issue, although readers were told there was a relative risk reduction in mortality, MI and stroke of 18% they were not also told that the absolute reduction was only 1.3%. The Appeal Board considered that it was misleading only to refer to relative risk reduction and upheld the Panel's ruling of a breach of the Code.

A general practitioner complained about a leavepiece (ref AC070946) for Competact (pioglitazone and metformin) and Actos (pioglitazone) issued by Takeda UK Limited. The claims at issue were referenced to Lincoff *et al* (2007) a meta-analysis to evaluate the effect of pioglitazone on ischaemic cardiovascular events which had been published in the Journal of the American Medical Association.

COMPLAINT

The complainant considered that the research data was presented in a misleading way. The advantages of pioglitazone were presented in relative risk reduction. The disadvantages were given in absolute risk reduction. If the absolute risk was portrayed in a relative risk format it meant that pioglitazone had an increase in serious heart failure of 25-30%.

When writing to Takeda, the Authority asked it to respond in relation to Clause 7.2 of the Code.

RESPONSE

Takeda stated that the leavepiece in question was generated in response to enquiries received about the effects of pioglitazone on cardiovascular risk factors and outcomes, following recent media coverage on glitazones and cardiovascular risk. The aim of the leavepiece was to share information from Lincoff *et al* 2007, thus allowing health professionals to gain further information on this important area.

Overall balance in terms of benefit:risk of pioglitazone in the leavepiece

In this respect the key findings of this meta-analysis were described in the highlighted yellow box of the leavepiece and had been specifically written in a sequential order to portray the following:

1 The primary endpoint of the meta-analysis: The beneficial effects of pioglitazone on mortality, myocardial infarction (MI) and stroke, with the statement:

'18% relative risk reduction seen with pioglitazone treatment in the composite primary outcome of mortality, MI or stroke compared with the control group'.

2 The potentially harmful effects of pioglitazone in terms of the associated heart failure that might be seen in some patients. For this, the statement taken from a secondary endpoint of the meta-analysis, was used:

'The meta-analysis showed an increase in serious heart failure with pioglitazone (2.3% vs 1.8%) but there was no corresponding increase in mortality'.

3 A succinct statement regarding the overall benefit:risk assessment with respect to the above three positive and one negative cardiovascular outcomes by means of a direct quote from the author that the results:

'… suggest that the net clinical cardiovascular benefit with pioglitazone therapy is favourable with an important reduction in irreversible events that is not attenuated by the risk of more frequent heart failure complications'.

4 The provision of clear prescribing advice, with the reminder that the presence of heart failure was a specific contraindication so as to ensure appropriate use of the medicine in the appropriate patient population. For this, the statement used was:

'Pioglitazone is indicated for the treatment of hyperglycaemia in type 2 diabetes and is contraindicated for use in patients with heart failure (NYHA class I-IV)'.

Lincoff et al

The stated objective of Lincoff *et al* was 'To systematically evaluate the effect of pioglitazone on ischaemic cardiac events' ie it was not specifically designed to evaluate heart failure. In the data extraction section of the paper, the primary outcome as well as the nature of the ischaemic cardiac events were further defined as 'The primary outcome was a composite of death, myocardial infarction or stroke'. Heart failure was only mentioned in the data extraction section of the abstract in terms of 'Secondary outcomes measures included the incidence of heart failure'. The use of the word 'incidence' was important as it was these incidence figures that were used in the leavepiece. In terms of portraying the potential harmful effects that might be seen with pioglitazone, the phrase 'The meta-analysis showed an increase in serious heart failure with pioglitazone (2.3% vs 1.8%) but there was no corresponding increase in mortality' was used. This succinctly summarised the results given in Table 3 of Lincoff *et al* relating to heart failure. As for the pre-specified secondary end point of 'serious heart failure' the incidence figures were 2.34% and 1.77% for the pioglitazone vs control group respectively, thus giving an absolute difference of 0.57% - numerically much smaller than the absolute difference for the primary endpoint (4.4% vs 5.7 %; 1.3% difference), yet conversely proffering a greater 'relative risk increase' (41%) than seen with the 'relative risk reduction' of the primary endpoint (18%). Thus the combination of two different hazard rates and relative risk reductions would not be appropriate, and could lead to further confusion on a topic that had already caused a lot of confusion with prescribers in 2007.

There had been numerous reports of data and media articles in 2007 on glitazones and associated cardiovascular risks, stemming from a meta-analysis (authored by the same group as this pioglitazone meta-analysis) published in May 2007 (Nissen *et al* 2007). Since then, there had been various reports on both the cardiovascular effects and heart failure for glitazones, which had proved confusing to prescribers. This was reflected by the increased number of enquiries Takeda had received regarding this subject this year. Therefore, Takeda submitted it was important to firstly accurately reflect this new data, whilst also not fuelling the confusion.

Lincoff *et al*, showed an 18% 'relative' risk reduction for the primary outcome and a 41% 'relative' risk increase for serious heart failure, which trended in an opposite direction to the 'absolute' risks for these same endpoints ie 0.57% increased 'absolute' risk for heart failure vs 1.3% reduced 'absolute' risk for the cardiovascular composite endpoint.

Hence for this summary of data depicted as a one-page leavepiece, the heart failure data was represented using the absolute figures only. Takeda believed this accurately reflected Lincoff *et al*, which stated 'This analysis also provides reassuring information that although fluid retention and heart failure are more frequent with pioglitazone treatment; the offsetting risks do not appear to negate the beneficial effects of the drug on irreversible ischaemic and fatal endpoints'.

The data was in-line and reflected the pioglitazone evidence base – eg PROactive showed a similar relative risk reduction for a similar cardiovascular composite endpoint (time to first event of mortality, MI or stroke (except silent MI); relative risk reduction 16% absolute risk reduction: 2.1%) endpoints, whereas the absolute increased risk for heart failure was again in line with that described by the European Medicines Evaluation Agency (EMEA) summary of product characteristics (SPC) which consistently depicted this information as an 'absolute' risk, with the PROactive study showing a 1.6% increase in risk with pioglitazone treatment compared to placebo.

Reference was also made to the combined secondary endpoint of 'Death/serious heart failure' as death was a key component of the combined primary outcome. In this instance the corresponding figures were 4.22% and 4.10% respectively p=0.77.

A recent case (Cases AUTH/1984/4/07 and AUTH/1985/4/07) had also questioned the use of 'relative' risk in instances where it could exaggerate the actual 'absolute' risk, however no breach was ruled.

Need for consistency in the reporting rates of serious heart

failure associated with pioglitazone

The data synthesis section of Lincoff *et al* reported the results for the primary outcome both in terms of absolute values as well as hazard ratios or relative risk reductions. For the heart failure data, the absolute values had also been chosen so as to ensure that they were in accordance with the figures used in PROactive and the SPC hence the statement 'These findings corroborate the results of the PROactive study together with the information in the pioglitazone licences'.

In the PROactive study the incidence of serious heart failure as defined by 'Heart failure requiring hospital admission' was 6% v 4% for pioglitazone v control (ref Table 9 Dormandy *et al*) and in the Actos SPC, Section 4.8 undesirable effects, post marketing data there was a statement 'In controlled clinical trials the incidence of reports of heart failure with pioglitazone treatment was the same as in placebo, metformin and sulphonyurea treatment groups, but was increased when used in combination therapy with insulin. In an outcome study of patients with pre-existing major macrovascular disease, the incidence of serious heart failure was 1.6% higher with pioglitazone than with placebo, when added to therapy that included insulin. However, this did not lead to an increase in mortality in this study'. At no point was there any mention of relative risk.

Reporting of safety information by the EMEA in terms of benefit:risk assessment

Most clinical trials were specifically designed to evaluate the potential clinical benefit that a product might demonstrate in a clearly defined patient population, with the accompanying safety information being collected as a secondary end-point. The primary end-point in clinical outcome studies was generally reported in terms of relative risk reduction and not as absolute risk, as was reflected in the European Public Assessment for pioglitazone where the EMEA in its assessment of pioglitazone in the PROactive study stated that 'The composite endpoints including the primary endpoint excluding silent MI and cardiovascular mortality or non-fatal MI (excluding silent MI) were also evaluated and resulted in relative risk reductions of 10% and 14% respectively for pioglitazone-treated patients, although these reductions were not statistically significant'.

In terms of its assessment of heart failure, the EMEA did not describe this in terms of relative risk reduction as the only statement was that 'Events of serious heart failure were reported more frequently in the pioglitazone group than in the placebo group; however, mortality was not increased in the pioglitazone-treated patients …. Within the cohort of patients receiving insulin at baseline in PROactive, a higher reporting rate of heart failure was seen (6.3% with pioglitazone in combination with insulin vs 5.3% with insulin alone) compared to the total study population (5.1% vs 4.1%)'.

In conclusion

As stated above, in this piece Takeda aimed to share with health professionals information from a recent publication of a meta-analysis of pioglitazone data designed specifically to investigate cardiovascular effects, in order that they would gain further information on this important area. The piece was developed because Takeda had received a large number of enquiries from health professionals about the effects of pioglitazone on cardiovascular risk factors and outcomes following media coverage on the glitazones and cardiovascular risk.

It was certainly never Takeda's intention to try and mislead anyone and it hoped that these comments would explain the thoughts behind the nature and content of the leavepiece and thus allay any concerns that the complainant might have had.

PANEL RULING

The Panel noted that the leavepiece contained, inter alia, two claims '18% relative risk reduction seen with pioglitazone treatment in the composite primary outcome of mortality, MI or stroke compared to the control group' and further down the page 'The meta–analysis showed an increase in serious heart failure with pioglitazone (2.3% vs 1.8%), but there was no corresponding increase in mortality' both of which were referenced to Lincoff *et al*.

The Panel noted that the 18% relative risk reduction in the composite outcome of mortality, MI or stroke was calculated from Lincoff *et al* (Table 3) which also provided the means to calculate the relative increased risk of serious heart failure (41% as submitted by Takeda). The overall absolute risk reduction in the primary end point was given as 4.38 % vs 5.74% and for serious heart failure as 2.34% vs 1.77%. The Panel noted that with regard to heart failure data the SPC did not refer to relative risk.

The Panel considered that the presentation of the data in the leavepiece was misleading. To provide one aspect of the information as a reduction in relative risk and another, the risk of serious heart failure, only as an increase in absolute risk was misleading as alleged. It was not made clear that the serious heart failure date represented an absolute risk. A breach of Clause 7.2 was ruled. This ruling was appealed.

During its consideration of this case the Panel was concerned about the heading 'Pioglitazone is the only glitazone with beneficial effects on cardiovascular risk and cardiovascular outcomes in Type 2 diabetes' in the light of the data on the increase in heart failure. In its view the claim was too general given the data and might be misleading. The Panel requested that the company be advised of its views in this regard.

APPEAL BY TAKEDA

Takeda submitted that the points made in its response still stood and formed part of its appeal. The leavepiece was developed in response to the number of

enquiries which the company had received due to the media coverage on the glitazones and cardiovascular risk and the confusion that existed regarding MI risk (reported with rosiglitazone) and heart failure risk (seen with both glitazones). Takeda had ensured that the overall benefit:risk profile of pioglitazone was represented and as such the key findings from the meta-analysis were presented sequentially. Hence because the stated objective of this meta-analysis was to systematically evaluate the effect of pioglitazone on ischaemic cardiovascular events defined as death, MI or stroke, this information was presented first. The secondary outcome measures included the incidence of serious heart failure and hence the potentially harmful effect of pioglitazone in terms of the incidence of associated heart failure was presented second. This accurately reflected Lincoff *et al* which stated 'This analysis also provides reassuring information that although fluid retention and heart failure are more frequent with pioglitazone treatment, the offsetting risks do not appear to negate the beneficial effects of the drug on irreversible ischaemic and fatal end points'. Next a succinct statement regarding the overall benefit:risk assessment with respect to the above three positive and one negative cardiovascular outcomes by means of a direct quotation from the author was used. Finally a reminder was included that the presence of heart failure was a specific contraindication so as to ensure appropriate use of the medicine in the appropriate patient population. Within the leavepiece a similar amount of space was used to report on the risks as the information on the benefits.

Takeda submitted that it was an accepted convention to use relative risk reduction and absolute risk to describe efficacy and safety/tolerability endpoints respectively. There was only one prospective, cardiovascular outcome study for pioglitazone; PROactive which not only formed part of the meta-analysis referred to above, but was also specifically referred to in the mailer. The results were described in terms of relative risk reduction for all the efficacy data with the safety/tolerability data similarly being given in percentages or absolute values. The statistical basis for this study and calculation of the required patient numbers was based on a projected 20% relative risk reduction between the pioglitazone and placebo treated groups. Consequently the primary endpoint was expressed in terms of hazard ratio/relative risk reduction. In contrast the safety evaluations of serious and non serious events were only shown in terms of percentages/absolute values. At no point was any attempt made to report the adverse effects of pioglitazone treatment in terms of a relative risk increase. The methodological design and results for the PROactive study were reported in Diabetes Care and the Lancet respectively.

Takeda submitted that the internationally acclaimed, landmark study in the field of diabetes was the UKPDS, and the results from this key long-term, prospective, outcomes study had changed treatment paradigms in type 2 diabetes. There had been 78 publications generated from this one study with one of the most important being UKPDS 38, where the effect of good glycaemic and blood pressure control on both micro and macrovascular outcomes was evaluated. In all instances the efficacy results were expressed in terms of relative risk reduction with the safety profile, of the two different treatment regimens, being given in percentages/absolute values.

Takeda submitted that in the EMEA European Public Assessment Record (EPAR) for pioglitazone, the various efficacy results from PROactive – the cardiovascular outcome study, were given in terms of relative risk reduction, yet the safety tolerability data was expressed in terms of percentages. Clearly in their assessment of the risk:benefit of the pioglitazone the regulatory agencies had chosen to use these two different approaches.

Takeda submitted that the Food and Drug Administration's decision to include a black box warning for pioglitazone for heart failure was based on the absolute values or percentages which had been seen in clinical trials for pioglitazone based on treatment regimens vs control therapy. A relative risk increase was never referred to.

Takeda submitted that when the EMEA updated the EPAR for the approval of the new renal indication for Aprovel (irbesartan) the benefit was described in terms of relative risk reduction and the common side effects in terms of incidence rates ie 1 in 10 or 1 in 100 and not relative risk. Finally the adverse effects in section 4.8 of all SPCs were referred to in terms in incidence rates or percentages and not in terms of relative risk with respect to efficacy.

Takeda submitted that it took great care and attention to address all of the matters in the leavepiece in question, in order to ensure it presented the information in a way that clearly showed the risk:benefit profile of the product.

In conclusion, Takeda submitted that as the use of relative risk reductions in clinical outcomes studies was an accepted method for describing efficacy, and the use of percentages or absolute values were accepted for use for the safety tolerability data, the leavepiece was not misleading either directly or by implication and therefore not in breach of Clause 7.2.

COMMENTS FROM THE COMPLAINANT

The complainant stated that he had not changed his opinion. Considering the meta-analysis by Lincoff *et al*, the primary outcome of death/MI/stroke had a hazard ration of 0.82 in favour of pioglitazone which equated to the 18% relative risk reduction in the leavepiece. This statistic was based on absolute risk of 5.7% v 4.4% which equalled an absolute risk reduction of 1.3%. A fair presentation of the data would be to put the advantages and disadvantages in the same format, eg 18% relative risk reduction (absolute risk reduction 1.3%) in death, MI or stroke with pioglitazone vs 41% relative risk of increase (absolute risk of increase 0.5%) in heart failure.

The complainant alleged that the above figures revealed relative risk reduction to be deceptive. The

figures also showed how inappropriate it was to mix relative risk and absolute risk. The selective use of 18% relative risk reduction whilst at the same time giving the disadvantages in absolute terms (for the reader to calculate) was designed to mislead. The benefits of pioglitazone were transparent when viewed in absolute terms.

The complainant appreciated that relative risk measures were widely used in research papers, (as in UKPDS 38) but this did not detract from the fact that relative risk and absolute risk were used as comparators on the same page of a promotional document.

The complainant submitted that the majority of his GP colleagues failed to detect the ambiguity within the statistical measures. When the full picture was explained the usual response was that of annoyance. Unfortunately, absolute and relative risk was not well understood by medical professionals making it difficult for them to apply risk data to individual patients. Consequently the profession was easily misled by relative risk data (McGettigan *et al* 1999). The position taken by Takeda saddened the complainant as it argued that it was common practice and therefore acceptable to juxtapose relative risk and absolute risk. Common practice did not imply right and proper practice. The leavepiece was one example of misleading promotional literature which used relative risk data to bias health professionals towards the prescription of medicines, which was sometimes against the patient's best interests. This problem could be reduced if relative risk data was always accompanied by absolute risk comparators in a standardised format, as illustrated above.

APPEAL BOARD RULING

The Appeal Board noted Takeda's submission regarding the way in which risks were conventionally reported in scientific papers, SPCs and the like. The leavepiece at issue, however, was a promotional item which thus had to meet the requirements of the Code. The leavepiece had, in effect, condensed the main findings of Lincoff *et al* to one sheet of A4 and in that regard it lacked the additional information which would have otherwise provided a context for the figures reported.

The Appeal Board noted that the leavepiece contained, inter alia, two claims '18% relative risk reduction seen with pioglitazone treatment in the composite primary outcome of mortality, MI or stroke compared to the control group' and further down the page 'The meta-analysis showed an increase in serious heart failure with pioglitazone (2.3% vs 1.8%), but there was no corresponding increase in mortality' both of which were referenced to Lincoff *et al*.

The Appeal Board noted that in the abstract of Lincoff *et al*, the data synthesis section detailed the statistical outcome of the study. The primary composite outcome of death, MI or stroke was reported in terms of absolute risk (4.4% for pioglitazone vs 5.7% for control) with a hazard ratio of 0.82 which had been translated into the leavepiece as an 18% relative risk reduction. The same set of figures was reported for the increased risk of serious heart failure (2.3% for pioglitazone vs 1.8% for control) only in this case the hazard ratio of 1.41 had not been translated into the leavepiece as a 41% relative increased risk. Thus, although the same set of data was reported for the two outcomes they had been reported differently in the leavepiece.

The Appeal Board noted that health professionals knowing only the relative risk of an event or events happening, without also knowing the absolute risks involved, would be unable to judge the clinical impact of the information presented; with regard to the above, although readers were told there was a relative risk reduction in mortality, MI and stroke of 18% they were not also told that the absolute reduction was only 1.3%. The Appeal Board considered that it was misleading only to refer to relative risk reduction and upheld the Panel's ruling of a breach of Clause 7.2. The appeal was unsuccessful.

Complaint received	**29 November 2007**
Case completed	**3 April 2008**

CASE AUTH/2078/1/08

HOSPITAL PHARMACIST v PFIZER

Promotion of Ecalta and Celsentri

A hospital pharmacist complained about a letter sent on behalf of Pfizer, which asked the recipient to add Ecalta and Celsentri to the list of available medicines on their electronic prescribing and dispensing system. The letter stated the products' names and their pharmaceutical form.

The complainant regarded the letter as an advertisement and queried whether it should have included prescribing information.

The Panel did not consider the letter in question met the exemption to the definition of promotion for 'factual, accurate, informative announcements and reference material concerning licensed medicines and relating, for example to pack changes, adverse-reaction warnings, trade catalogues and price lists, provided they include no product claims'. The letter was not an announcement, it asked the recipient to facilitate the addition of Ecalta and Celsentri to the list of currently available medicines on the local electronic prescribing and dispensing system. The Panel considered that soliciting such an action would promote the prescription supply, sale or administration of the products. In that regard the Panel noted Pfizer's submission that much of the tracking of ordering, supply, prescribing and dispensing of medicines in secondary care was conducted using computer-based systems. The Panel thus considered that the letter promoted Ecalta and Celsentri and in that regard should have included the prescribing information for each. As no prescribing information was included a breach of the Code was ruled.

A hospital pharmacist complained about a letter he had received on behalf of Pfizer Limited. The letter asked the recipient if they could add Ecalta and Celsentri to the list of available medicines on their electronic prescribing and dispensing system. The letter stated the products' names and their pharmaceutical form. The reader was advised that further information, including full monographs and summaries of product characteristics, were available from Pfizer.

COMPLAINT

The complainant regarded the letter as an advertisement telling him of the availability of two new products and as such queried whether it should have included prescribing information.

When writing to Pfizer the Authority asked it to bear in mind the requirements of Clause 4.1 of the Code.

RESPONSE

Pfizer noted that Clause 4.1 required prescribing information to be provided on all promotional material for a medicine except for abbreviated advertisements and certain promotional aids. Clause 1.2 defines promotion as '… any activity undertaken by a pharmaceutical company or with its authority which promotes the prescription, supply, sale or administration of its medicines'.

In addition, Clause 1.2 listed a number of types of materials and activities which were not covered by this definition, including, '… factual, accurate, informative announcements and reference material concerning licensed medicines and relating, for example, to pack changes, adverse reactions warnings, trade catalogues and price lists, provided they include no product claims'.

Pfizer submitted that much of the tracking of ordering, supply, prescribing and dispensing of medicines in secondary care was conducted using computer-based systems. For such systems to function efficiently all currently available medicines had to be listed appropriately and the databases updated when new medicines became available. Pfizer explained that it had used the services of a specialist agency to ensure that information pharmacists responsible for updating these databases knew that Ecalta and Celsentri were available.

Pfizer considered that the agency had fulfilled its responsibilities in these respects and that neither the method of communication nor the letter itself could be interpreted as promotional. Pfizer therefore did not consider that it was necessary to include prescribing information.

In summary, Pfizer considered that the letter in question was not promotional, as defined by Clause 1.2 of the Code, and therefore the requirements for prescribing information as set out in Clause 4.1 did not apply and no breach of the Code had occurred.

PANEL RULING

The Panel noted that amongst those items not regarded as being promotional under the Code were 'factual, accurate, informative announcements and reference material concerning licensed medicines and relating, for example to pack changes, adverse-reaction warnings, trade catalogues and price lists, provided they include no product claims' (Clause 1.2 refers). The Panel did not consider the letter in question met this exemption to the definition of promotion. The letter was not an announcement, it was a request for

the recipient to facilitate the addition of Ecalta and Celsentri to the list of currently available medicines on the local electronic prescribing and dispensing system. The Panel considered that soliciting such an action would promote the prescription supply, sale or administration of the two products. In that regard the Panel noted Pfizer's submission that much of the tracking of ordering, supply, prescribing and dispensing of medicines in secondary care was conducted using computer-based systems. The Panel thus considered that the letter promoted Ecalta and Celsentri and in that regard should have included the prescribing information for each. As no prescribing information was included a breach of Clause 4.1 was ruled.

Complaint received 15 January 2008

Case completed 14 February 2008

CASE AUTH/2079/1/08 and CASE AUTH/2080/1/08 *NO BREACH OF THE CODE*

ROCHE and GLAXOSMITHKLINE v SANOFI-AVENTIS and PROCTER & GAMBLE

Actonel exhibition panel

Roche and GlaxoSmithKline alleged that an exhibition panel for Actonel (risedronate) used by Sanofi-Aventis and Procter & Gamble (the Alliance for Better Bone Health, ABBH) contained claims which were inconsistent with the summary of product characteristics (SPC) and used data outwith the product licence.

Actonel 5mg was for once daily administration and Actonel 35mg was for once weekly administration. Both products were indicated for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral fractures and treatment of established postmenopausal osteoporosis, to reduce the risk of hip fractures. In addition Actonel 5mg was indicated in the prevention of osteoporosis in postmenopausal women with increased risk of osteoporosis and in postmenopausal women undergoing long-term systemic corticosteroid treatment. Actonel 35mg was indicated for the treatment of osteoporosis in men at high risk of fracture. Roche and GlaxoSmithKline co-marketed Bonviva (ibandronate) for the treatment of postmenopausal osteoporosis.

Bisphosphonates had a well established safety profile and their effects on the gastrointestinal tract were understood. The SPCs for all the bisphosphonates included a statement under special warnings and precautions for use relating to GI tolerability. The relevant section of the Actonel SPC stated:

'Some bisphosphonates have been associated with oesophagitis and oesophageal ulcerations. Therefore patients should pay attention to the dosing instructions (see section 4.2). In patients who have a history of oesophageal disorders which delay oesophageal transit or emptying e.g. stricture or achalasia, or who are unable to stay in the upright position for at least 30 minutes after taking the tablet, risedronate sodium should be used with special caution because of limited clinical experience in these patients. Prescribers should emphasise the importance of the dosing instructions to these patients.'

Roche and GlaxoSmithKline alleged that the exhibition panel contradicted the warnings and special precautions for use within the Actonel SPC. Although the exhibition panel had the statement from the SPC within it, it appeared as a footnote, in small text within a box dedicated to a single trial rather than prominent and associated with the high level claims made in the exhibition panel.

Taggart *et al* was a pooled analysis of 9 studies that used Actonel 5mg daily. Very little Actonel 5mg was prescribed in the UK; the significant majority of patients took 35mg once weekly. Unlike efficacy measures, safety data could not simply be bridged from one formulation to another, particularly in the case of bisphosphonates which had been specifically formulated in longer interval dose formulations to avoid the adverse effects and inconvenience associated with dosing. Of specific concern was that the data presented included a proportion (1.7%) of patients in which Actonel could not be prescribed because, inter alia, they were either male or premenopausal.

Overall Roche and GlaxoSmithKline believed that the ABBH had used inconsistent safety messages in promotional material that could potentially mislead prescribers and adversely impact patient safety.

The Panel examined the exhibition panel which was headed 'In postmenopausal osteoporosis' followed by 'Tailor your osteoporosis therapy to your individual patients' needs'. This was followed by a section referring to patients taking concomitant medication (aspirin/NSAID/proton pump inhibitor (PPI)) or having a history of or current GI illness (excluding conditions which delayed oesophageal transit or emptying). The subject of the exhibition panel was thus a specific subset of patients with postmenopausal osteoporosis. A large box headed 'Actonel 5mg daily' stated that in patients who regularly took acetyl salicylic acid or NSAIDs on 3 or more days per week the incidence of upper GI adverse events in such patients was similar to that in control patients. This statement, which appeared in both the Actonel 5mg and 35mg SPCs, was followed by a bar chart referenced to Taggart *et al* headed 'Actonel's upper GI tolerability profile in patients at risk of upper GI side effects in clinical trials of up to 3 years duration'. A footnote to the bar chart stated that Taggart *et al* included 1.7% of the population that were men or premenopausal women and that these patient groups were not licensed for treatment with Actonel 5mg. Beside the bar chart was a prominent statement that in the Actonel 5mg Phase III trials, patients were not excluded because of previous or current GI illness or use of medicines associated with GI intolerance such as NSAIDs or aspirin, (Reginster *et al* 2000 and Harris *et al* 1999). The box also included the bisphosphonates class warning which again appeared in both Actonel SPCs.

Taggart *et al* concluded that treatment with 5mg risedronate did not result in higher frequency of

upper GI tract events amongst patients who had active GI tract disease or required treatment with gastric antisecretory medicines or patients who were receiving concomitant treatment with aspirin or NSAIDs. To establish the applicability of these findings to clinical practice it would be important to have comprehensive postmarketing data on risedronate.

The Panel noted that neither the Actonel 5mg SPC nor the Actonel 35mg SPC included any warnings advising against concomitant use of NSAIDs, whereas Section 4.4 of the Bonviva (150mg) SPC stated 'Since NSAIDs and bisphosphonates are both associated with gastrointestinal irritation, caution should be taken during concomitant administration'.

The Panel noted that the exhibition panel referred generally to patients taking concomitant medicine likely to cause GI problems or with a history of or current GI illness. It then went on to refer only to the 5mg dose. Health professionals would be aware of the dosing instructions for bisphosphonates and in that regard noted the complainants' submission that the effects of biphosphonates on the GI tract were well understood.

The Panel considered that the exhibition panel was clear that the data related to Actonel 5mg. It noted the complainants' view that this was a rarely used dose. The Panel did not accept that the exhibition panel stated or implied that data from the 5mg applied to the 35mg dose as alleged even though in some cases it did for example, the class warning and the statement regarding regular acetyl salicylic acid or NSAID users. There was no mention of the 35mg dose. The 35mg Actonel SPC stated that in a one year study of postmenopausal women with osteoporosis the overall safety and tolerability profiles of the 5mg daily dose and the 35 mg weekly dose were similar. It added, however, that investigators reported a greater incidence in GI disorder (1.6% vs 1%) for 35mg Actonel compared to the 5mg dose.

The Panel noted that Taggart *et al* included patients (1.7% of the population) who were not within the licensed indication for Actonel 5mg. The data was used in relation to tolerability not efficacy. The exhibition panel only included photographs of older (ie postmenopausal) women and was headed 'In postmenopausal women …' in the circumstances the Panel did not consider that the data promoted the use of Actonel 5mg in unlicensed patient populations as alleged. The Panel ruled no breach of the Code.

The Panel considered the exhibition panel was not inconsistent with the Actonel 5mg SPC; no breach of the Code was ruled.

The Panel did not consider that the information about side effects failed to reflect current evidence. The SPC warning was included. Nor did it fail to encourage rational use. Thus no breach of the Code was ruled.

The Panel considered that the bisphosphonate class warning about special caution when using Actonel in certain patients might have been more prominent, ie appear in the same section as the information about patients who regularly used aspirin and NSAIDs, nonetheless it did not consider that in the circumstances it was misleading for it to appear where it had. No breach of the Code was ruled.

Roche Products Limited and GlaxoSmithKline UK Ltd complained about an exhibition panel (ref ACT 3664) for Actonel (risedronate) used by Sanofi-Aventis and Procter & Gamble Pharmaceuticals UK Ltd (the Alliance for Better Bone Health, ABBH). The exhibition panel was displayed at the British Society of Geriatrics meeting held in Harrogate (21-23 November 2007) and the National Osteoporosis Society meeting in Edinburgh (26-28 November 2007).

Actonel 5mg was for once daily administration and Actonel 35mg was for once weekly administration. Both products were indicated for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral fractures and treatment of established postmenopausal osteoporosis, to reduce the risk of hip fractures. In addition Actonel 5mg was indicated in the prevention of osteoporosis in postmenopausal women with increased risk of osteoporosis and in postmenopausal women undergoing long-term systemic corticosteroid treatment. Actonel 35mg was indicated for the treatment of osteoporosis in men at high risk of fracture.

Roche and GlaxoSmithKline co-marketed Bonviva (ibandronate) for the treatment of postmenopausal osteoporosis.

COMPLAINT

The claims in question related to the use of Taggart *et al* (2002) and the inappropriate use of safety data in high level promotional claims which were originally noted in an Actonel leavepiece (ACT3543).

The basis of the concerns remained around the use of claims about safety that were inconsistent with the Actonel summary of product characteristics (SPC) and the use of data in promotional material that contained data outside the product's licence.

Bisphosphonates as a class were associated with a well established safety profile. The effects of bisphosphonates on the gastrointestinal tract were well understood. The SPCs for all the bisphosphonates included a statement under special warnings and precautions for use relating to GI tolerability. The relevant section of the Actonel SPC stated:

> 'Some bisphosphonates have been associated with oesophagitis and oesophageal ulcerations. Therefore patients should pay attention to the dosing instructions (see section 4.2). In patients who have a history of oesophageal disorders which delay oesophageal transit or emptying e.g. stricture or achalasia, or who are unable to stay in the upright position for at least 30 minutes after taking the tablet, risedronate sodium should be used with

special caution because of limited clinical experience in these patients. Prescribers should emphasise the importance of the dosing instructions to these patients.'

Roche and GlaxoSmithKline alleged that the leavepiece and the exhibition panel, contradicted the warnings and special precautions for use within the Actonel SPC. It was recognised that the exhibition panel had the statement from the SPC within it however it was a footnote, in small text within a box dedicated to a single trial rather than prominent and associated with the high level claims made in the exhibition panel. The companies did not believe that this small footnote met the assurances or their concerns and was not in keeping with the spirit of the Code when ABBH stated that it would review the materials in the light of discussions.

Taggart *et al* was a pooled analysis of 9 studies that used Actonel 5mg daily. This 5mg dose made up a very small proportion of the actual Actonel prescribed in the UK. The significant majority of patients took 35mg once weekly. In 'quarter 2' of 2007 IMS data showed that 96.6% of scripts written in the community were for the weekly preparation and only 3.4% for the daily 5mg dose. Unlike standard or surrogate efficacy measures, safety data could not simply be bridged from one formulation to another, particularly in the case of bisphosphonates which had been specifically formulated in longer interval dose formulations to avoid the adverse effects and inconvenience associated with dosing. Of specific concern was that the data presented included a proportion (1.7%) of patients in which Actonel could not be prescribed, ie they were either male or premenopausal. The licensed indications for Actonel 5mg daily did not include the treatment of osteoporosis in either of these patient groups. Additionally the following groups included in Taggart *et al* were out of licence for Actonel 35mg weekly: pre- and postmenopausal women with, or at risk of, corticosteroid-induced osteoporosis, males with, or at risk of, corticosteroid-induced osteoporosis.

The ABBH asserted that stating these facts within the material, in very small font as a footer, allowed it to use these data and address Roche and GlaxoSmithKline's previous concerns. The ABBH also believed that this was permissible as it related to safety. Roche and GlaxoSmithKline accepted in the context of balanced material or material that was non promotional, that such data were valid and assisted the prescriber. In this case however these data were being used to support prominent and high level claims for the use of a medicine in patients who would in all probability receive the weekly rather than the daily dose and in whom special consideration for the GI adverse effects of bisphosphonates must be considered. Roche and GlaxoSmithKline believed the addition of a small footer on a large exhibition panel with a prominent claim did not meet the assurances given in intercompany dialogue.

Overall Roche and GlaxoSmithKline believed that the ABBH had used inconsistent safety messages in promotional material that could potentially mislead prescribers and adversely impact patient safety.

Breaches of Clauses 3.2, 7.2, 7.9 and 7.10 of the Code were alleged.

RESPONSE

Sanofi-Aventis and Procter & Gamble submitted a joint response as the ABBH.

The ABBH noted that Roche and GlaxoSmithKline referred to two meetings but they only referred to one exhibition panel ACT3664. In fact, ACT3664 was shown at the Harrogate meeting and an amended exhibition panel, ACT3599 was shown at the Edinburgh meeting.

At both meetings, which were national scientific congresses, these exhibition panels were shown at the Actonel booth, which was in an exhibition hall, and amongst those from other companies involved in osteoporosis management. The exhibition panels were certified solely for use at these congresses and were thus no longer in use.

The ABBH had taken every opportunity to enter into dialogue with Roche and GlaxoSmithKline including sending copies of the exhibition panel for them to review. This was clear evidence of transparency. The ABBH considered it had done everything possible to maintain a healthy intercompany dialogue and had not misled Roche and GlaxoSmithKline.

The ABBH noted that the main basis for the allegation that tolerability data in the exhibition panels was inconsistent with the SPC for Actonel (specifically in relation to Section 4.4 of the SPC) appeared to be what Roche and GlaxoSmithKline inappropriately referred to as a 'footnote'. This explanatory text was immediately adjacent to the bar chart presenting data and appeared in the same field of vision for the reader. The text was taken directly from Section 4.4 of the Actonel SPC and provided necessary information for health professionals to make an informed decision on their choice of therapy:

'Bisphosphonates have been associated with oesophagitis and oesophageal ulcerations. Therefore patients should pay attention to the dosing instructions. In patients who have a history of oesophageal disorders which delay oesophageal transit or emptying e.g. stricture of achalasia, or who are unable to stay in the upright position for at least 30 minutes after taking the tablet, risedronate sodium should be used with special caution because of limited clinical experience in these patients. Prescribers should emphasise the importance of the dosing instructions to these patients'.

Given the prominence of this text within the exhibition panel used in Harrogate and the overall size of the panel (1.95 metres high x 3.28 metres wide), the text in question was very clear (font size of 1.11cm and the height of the paragraph in question was approximately 0.15 metres). The same could be said for the exhibition panel used in Edinburgh (an overall size of 2.4 metres

high x 4 metres wide, with a font size of the text in question of 1.86cm and the height of the paragraph in question was approximately 0.25 metres).

Additionally, from the wording, health professionals were advised to exclude postmenopausal women with osteoporosis with conditions which delayed oesophageal transit or emptying when considering whether treatment was appropriate.

It should also be noted that Section 5.2 of the SPC for Actonel also stated that 'Among regular acetyl salicylic acid or NSAID users (3 or more days per week) the incidence of upper gastrointestinal adverse events in Actonel treated patients was similar to that in control patients'.

The ABBH considered that sharing these tolerability data in the exhibition panels was not inconsistent with the Actonel SPC and therefore not in breach of the Code.

The ABBH noted that Roche and GlaxoSmithKline had alleged that the tolerability data in the exhibition panels referred to some patients who were outside of the terms of the Actonel licence and also that safety data could not be bridged from one formulation to another.

The ABBH noted that this latter point had not been raised during the intercompany dialogue, nor had the ABBH made or inferred bridging of safety data between dosages. The data included in both exhibition panels was for the Actonel 5mg dosage only and was clearly labelled so.

That said, the Actonel 35mg SPC stated:

> '… comparing risedronate sodium 5mg daily … and risedronate 35mg weekly … in postmenopausal women with osteoporosis, the overall safety and tolerability profiles were similar'.

Given that these data had been reviewed by the regulatory authorities which approved the text in the SPC and the ABBH had not made any bridging statements on safety, the complainants' comments were inappropriate and the ABBH considered that the Code had not been breached.

With regard to the issue that the data presented included a proportion of patients not currently within the licence for Actonel (1.7% of the population were either male or premenopausal women), the ABBH stated that these were tolerability data, not efficacy. It was important to ensure health professionals saw balanced and robust data and it would be inconceivable to prohibit sharing of an analysis such as that by Taggart *et al* when 98.3% of the overall population was within the product licence.

Taggart *et al* conducted a pooled analysis including 9 randomised, double-blind, placebo-controlled, parallel group, Phase 3 studies of the risedronate clinical program. This included over 10,000 patients.

It was clearly stated on the exhibition panels that 1.7% of the population included in Taggart *et al*, were male or premenopausal women and that these were not patient populations included in the product licence for Actonel 5mg.

The exhibition panels did not encourage the prescription of Actonel to patient populations outside the product licence. To clarify this point, the top of the exhibition panel stated that the population referred to was postmenopausal osteoporosis.

It was clear that in the context of a piece about tolerability that this information was included for transparency to allow health professionals to fully assess the validity of the data and was obviously not presented to encourage use of Actonel in these populations.

The ABBH strongly believed it had done all it could to have open and transparent intercompany dialogue and regretted that Roche and GlaxoSmithKline had considered it necessary to escalate this to the Authority.

The ABBH hoped it had addressed all the elements that suggested breaches of Clauses 3.2, 7.2, 7.9 and 7.10 with regard to exhibition panels at issue.

PANEL RULING

The Panel examined exhibition panel ACT3664. There was no complaint regarding ACT3599. Exhibition Panel ACT3664 was headed 'In postmenopausal osteoporosis' followed by 'Tailor your osteoporosis therapy to your individual patients' needs'. This was followed by a section referring to patients taking concomitant medication (aspirin/NSAID/proton pump inhibitor (PPI)) or having a history of or current GI illness (excluding conditions which delayed oesophageal transit or emptying). The subject of the exhibition panel was thus a specific subset of patients with postmenopausal osteoporosis. A large box headed 'Actonel 5mg daily' stated that in patients who regularly took acetyl salicylic acid or NSAIDs on 3 or more days per week the incidence of upper GI adverse events in such patients was similar to that in control patients. This statement, which appeared in both the Actonel 5mg and 35mg SPCs, was followed by a bar chart referenced to Taggart *et al* headed 'Actonel's upper GI tolerability profile in patients at risk of upper GI side effects in clinical trials of up to 3 years duration'. A footnote to the bar chart stated that Taggart *et al* included 1.7% of the population that were men or premenopausal women and that these patient groups were not licensed for treatment with Actonel 5mg. Beside the bar chart was a prominent statement that in the Actonel 5mg Phase III trials, patients were not excluded because of previous or current GI illness or use of medicines associated with GI intolerance such as NSAIDs or aspirin, (Reginster *et al* 2000 and Harris *et al* 1999). The box also included the bisphosphonates class warning which again appeared in both Actonel SPCs.

Taggart *et al* concluded that treatment with 5mg risedronate did not result in higher frequency of upper GI tract events amongst patients who had active GI tract disease or required treatment with gastric

antisecretory medicines or patients who were receiving concomitant treatment with aspirin or NSAIDs. To establish the applicability of these findings to clinical practice it would be important to have comprehensive postmarketing data on risedronate.

The Panel noted that neither the Actonel 5mg SPC nor the Actonel 35mg SPC included any warnings advising against concomitant use of NSAIDs, whereas Section 4.4 of the Bonviva (150mg) SPC stated 'Since NSAIDs and bisphosphonates are both associated with gastrointestinal irritation, caution should be taken during concomitant administration'.

The Panel noted that the exhibition panel referred generally to patients taking concomitant medicine likely to cause GI problems or with a history of or current GI illness. It then went on to refer only to the 5mg dose. Health professionals would be aware of the dosing instructions for bisphosphonates and in that regard noted the complainants' submission that the effects of biphosphonates on the GI tract were well understood.

The Panel considered that the exhibition panel was clear that the data related to Actonel 5mg. It noted the complainants' view that this was a rarely used dose. The Panel did not accept that the exhibition panel stated or implied that data from the 5mg applied to the 35mg dose as alleged even though in some cases it did for example, the class warning and the statement regarding regular acetyl salicylic acid or NSAID users. There was no mention of the 35mg dose. The 35mg Actonel SPC stated that in a one year study of postmenopausal women with osteoporosis the overall safety and tolerability profiles of the 5mg daily dose and the 35 mg weekly dose were similar. It added, however, that investigators reported a greater incidence in GI disorder (1.6% vs 1%) for 35mg Actonel compared to the 5mg dose.

The Panel noted that Taggart *et al* included patients (1.7% of the population) who were not within the licensed indication for Actonel 5mg. The data was used in relation to tolerability not efficacy. The exhibition panel only included photographs of older (ie postmenopausal) women and was headed 'In postmenopausal women …' In the circumstances the Panel did not consider that the data promoted the use of Actonel 5mg in unlicensed patient populations as alleged. The Panel ruled no breach of Clause 3.2.

The Panel considered the exhibition panel was not inconsistent with the Actonel 5mg SPC; no breach of Clause 3.2 was ruled.

The Panel did not consider that the information about side effects failed to reflect current evidence. The SPC warning was included. Nor did it fail to encourage rational use. Thus no breaches of Clauses 7.9 and 7.10 were ruled.

The Panel considered that the bisphosphonate class warning about special caution when using Actonel in certain patients might have been more prominent, ie appear in the same section as the information about patients who regularly used aspirin and NSAIDs, nonetheless it did not consider that in the circumstances it was misleading for it to appear where it had. No breach of the Code was ruled.

Complaint received 17 January 2008

Case completed 29 February 2008

CASE AUTH/2081/1/08

PRIMARY CARE TRUST PHARMACIST v TEVA

Guidelines in Practice supplement

A pharmacist at a primary care trust (PCT) complained that a supplement sent in association with the electronic edition of Guidelines in Practice and entitled 'Making an informed choice A guide to changing to CFC-free beclometasone inhalers' was disguised promotion for Qvar (CFC-free beclometasone diproprionate (BDP)). The article had been written by a programme director, medicines management, at a PCT. The supplement stated on the front cover that it was supported by an unrestricted educational grant from Teva UK Ltd. Prescribing information for Qvar appeared on the inside back page.

The complainant stated that the title suggested an independent review of the options. The choice of author, a PCT pharmacist, also implied impartiality. However, although some content was good, the complainant found on balance the supplement favoured Qvar more than would be expected from an impartial review. The complainant noted that an 'unrestricted' educational grant from Teva was referred to on the front cover which also directed readers to 'prescribing information' on the inside back page. Only the prescribing information for Qvar was included and not for the alternative product Clenil Modulite.

The Panel noted that the sponsors of the supplement Teva, had commissioned an agency to work with a key opinion leader to create it. The agency had contacted the author. The article was reviewed by Teva and went through its approval process to ensure compliance with the Code. Teva had paid to have copies distributed as a supplement to Guidelines in Practice.

The Panel considered that Teva was inextricably linked to the production of the supplement. There was no arm's length arrangement between the provision of the sponsorship and the generation of the supplement. Teva's agency and the commissioned author produced the article. The company had paid for it to be distributed. Given the company's involvement the Panel considered that the supplement was, in effect, a paid for insert which promoted Qvar.

The Panel considered that it was disguised promotion in that the insert appeared to be independent of Teva which was not so. The statement on the front cover 'Supported by an unrestricted educational grant from Teva UK Ltd' added to this impression and did not fairly reflect the actual arrangements. A breach of the Code was ruled.

A Primary Care Trust pharmacist complained about a supplement (ref HDM/07/047) sent in association with the electronic edition of Guidelines in Practice and entitled 'Making an informed choice A guide to changing to CFC-free beclometasone inhalers'. The article had been written by a programme director, medicines management, at a PCT. The supplement stated on the front cover that it was supported by an unrestricted educational grant from Teva UK Ltd. Prescribing information for Qvar (CFC-free beclometasone diproprionate (BDP)) appeared on the inside back page.

COMPLAINT

The complainant stated that the title of the supplement suggested an independent review of the options. The choice of author, a PCT pharmacist, also implied impartiality. However, although some content was good, the complainant found on balance the supplement favoured Qvar more than would be expected from an impartial review. The complainant noted that an 'unrestricted' educational grant from Teva was referred to on the front cover which also directed readers to 'prescribing information' on the inside back page. Only prescribing information for Qvar was included and not for the alternative product Clenil Modulite.

The complainant alleged that the supplement was actually an advertisement for Qvar and should not be circulated under the guise of an 'informed' independent prescribing guideline.

When writing to Teva, the Authority asked it to respond in relation to Clause 10.1 of the Code.

RESPONSE

Teva submitted that the article was clearly written by the stated author and not a third party and it complied with the requirements of the Code.

The author, a programme director, medicines management, to a PCT, agreed to write the article and was engaged by Teva's agency. The agency was paid to complete this project, and the fees paid to the author were negotiated directly between the two parties.

Teva had no part in creating the article after agreeing the initial brief. The article was prepared by the author and the agency. At the outset it was agreed that the document would have to go through the Teva approval process for promotional and educational material prior to publication. Throughout the process Teva never communicated directly with the author.

Guidelines in Practice was selected to distribute the article based on an evaluation of its readership for appropriateness of audience and a fee was paid. The editor made some minor suggestions for alterations to the article 'Making an informed choice', which were accepted by the author and reviewed via the Teva approval process. Final approval was granted on 6 September.

Teva submitted that the author chosen by the agency was suitably qualified to write such an article, and was selected as he was an opinion leader who had worked on a transition to CFC-free BDP inhalers and had extensive experience of this subject area. Teva disputed that the title and the choice of the author suggested either an independent review or an impression of impartiality, but rather it suggested an article that discussed the author's opinions and experiences with regard to a guide to changing to CFC-free BDP inhalers.

Teva noted the complainant's comment that 'The choice of author, a PCT pharmacist, also implied impartiality'. Teva considered that this was an emotional comment cleverly used to make the reader believe the article was not impartial but did not provide any data or facts as to why the complainant might believe this to be the case. Teva queried why the complainant considered that the article was not impartial. The company could not understand the comment and requested that if the matter was to be pursued then some detailed reasoning to support this allegation should be provided to enable it to mount a robust defence.

Teva noted that the supplement clearly stated at the outset that it was sponsored by an unrestricted educational grant from Teva. Therefore the opinions expressed in the article were the author's not Teva's.

Teva found the complainant's comment that although some content was good, on balance the supplement favoured Qvar more than would be expected from an impartial review most worrying; it appeared to suggest that the complainant had neither analysed the article in detail nor had the required knowledge to make such a judgement. The article was carefully written using published studies and the author ensured there was equal mention of both Qvar and Clenil where data were available. There were however two sections where Qvar was mentioned and Clenil was omitted. This was not due to bias on the part of the author but simply that Clenil Modulite was only available as a metered dose inhaler (MDI) and did not have any breath actuate inhalers (BAI) in its range of product. Further Trinity-Chiesi had not conducted any studies with Clenil Modulite recording patient reported outcomes such as quality of life and the occurrence of symptom-free days and therefore the product was not discussed in these sections apart from stating that no studies had been conducted.

Teva analysed the content of the supplement and noted the following:

Page 1 (title page): There was no mention of either product

Page 2: There was equal mention of both products

In a table of data it was clearly stated that Qvar was licensed for patients aged 12 years and over and Clenil Modulite was licensed for adults and children, but that patients under the age of 15 years required a volumatic spacer.

Page 3: A comparison of the two products was a fair and accurate reflection of both summaries of product characteristics (SPCs).

Page 3/4: A section regarding delivery devices discussed the benefits of BAIs compared with MDIs and the role of patient compliance. This section related to device and did not discuss either Qvar or Clenil in detail.

Page 4: A discussion of the different particle sizes of medicines was fully referenced and thus was accurate and complied with the Code.

Page 5 (clinical trial evidence): This section was divided into 2 parts which were clearly identified to discuss, in detail, clinical trial evidence of both Qvar and Clenil Modulite; the section relating to Clenil was substantially longer than the Qvar section (46 lines of text vs 35).

Each of these sections reviewed all published studies. In the Qvar section three short-term studies were reported (Magnussen 2000, Gross *et al* 1999 and Davies *et al* 1998) which indicated that Qvar had similar efficacy to CFC-BDP and these were clearly identified as short-term studies. This was followed by a more detailed discussion of the 12 month study (Fireman *et al* 2001) in which patients, who had stable asthma for one month were randomized to receive Qvar or CFC-BDP. The results were accurately depicted and it was clearly stated that there was no difference in peak expiratory flow rate or forced expiratory volume in one second between the groups but as the patients had stable asthma at entry a difference would not be expected. The study utilised a 3:1 randomisation to ensure that a large cohort of patients received Qvar.

The results from the study were also analysed by Price *et al* (2002) and these demonstrated a highly statistically significant difference in the number of symptom-free days between the groups (p=0.006). Teva noted that Price *et al*, as described in the article, used the data generated from the 12-month study for this analysis and did not conduct a separate 12 month study.

The Clenil Modulite section reported five clinical studies that were identified by literature search, four in adults and one in children. The studies lasted either 6 or 12 weeks; there were no studies of a longer duration.

Page 6 (quality of life): This section started by indicating that no studies had been conducted with Clenil Modulite so it clearly stated to the reader that no data were available for which a comparison could be made. The section then discussed Juniper *et al* (2002) in which the quality of life assessment (AQLQ) was reported over a 12 month period. This study was accurately reported indicating that the 'mean AQLQ score improved at each time point' and there was statistically significant improvement at 12 months.

The difference was marked between the two treatments and often there was some confusion as to how the results should be interpreted, but this was clearly described by the authors. The treatment difference between the two study populations was 0.24 and many commentators suggested that this was below the threshold of significance of 0.5. This was an incorrect interpretation of the results because the AQLQ was developed by Juniper and the threshold of 0.5 referred to the clinically meaningful change in any individual and could not be applied to an overall population. Juniper *et al* clearly stated that 'However to reject these results as being clinically unimportant would be erroneous, since the difference of 0.24 only represents the difference between mean values and does not take into account the heterogeneity of patient's response to the interventions'. This was appropriately referenced and as many patients had changed in excess of 0.5 a number needed to treat of between 7-8 was calculated which compared favourably with single digit changes between salmeterol and salbutamol. Indeed Juniper *et al* stated that 20-30% of patients admitted into the study had AQLQ scores of >6 on the 7 point scale and therefore had little ability to improve as the trial progressed. The authors' view that these changes were clinically meaningful was reinforced in the title of the article which Teva noted was published in a peer reviewed journal and the independent referees and the editorial board of the journal must also have agreed with the title 'Clinically important improvements in asthma-specific quality of life, but no difference in conventional indexes in patients changed from conventional BDP to approximately half the dose of extrafine BDP'.

When interpreting results it was important that they were taken in context and Juniper *et al*, when discussing the above results clearly stated that an earlier study that was conducted in just over 100 patients and for a period of 3 months only demonstrated a trend in favour of improved AQLQ results with extrafine BDP but noted that this did not reach statistical significance.

The 12 week study of Juniper *et al* (1999) was also cited in the article at issue.

Page 6/7/8 (changing to CFC-free inhalers): This detailed section discussed the roles of Qvar and Clenil equally and was fully referenced. The discussions were prefaced by a section indicating the measures that might be required such as extra-clinics and asthma reviews followed by an algorithm that in the opinion of the author provided rational decision making process map. Where it was possible to choose Clenil Modulite or Qvar both were mentioned but in situations where a BAI was needed the device that could be considered was mentioned and in some cases this was Qvar Easi-Breathe or Qvar Autohaler.

Teva submitted that manuscripts were selected for inclusion using standard selection criteria for writing a medical review article. It was usual practice to select manuscripts for inclusion that provided a definitive answer but it was not possible to add published references owing to the large numbers of publications in the field of asthma.

Teva submitted that it had demonstrated from the above that the supplement at issue was fair and balanced and thus complied with the Code. If the reader took from the articles that there were benefits in favour of Qvar compared with Clenil then that was only because long-term clinical studies had indeed shown clinical benefit for patients receiving Qvar compared with CFC-BDP but no such comparison could be made with Clenil Modulite as no long-term studies had been conducted.

Teva submitted that the complainant's comment that they expected to see the prescribing information for Clenil Modulite, as well as that of Qvar, indicated that the complainant was unaware of the UK regulations where the sponsoring company should provide prescribing information for its own product but there was no requirement to contain prescribing information from a competitor company. Indeed if this was the case then all articles would need approval from competitors to proceed as the prescribing information was the copyright of the company and all uses would need prior approval as well as sign off against the Code and the SPC in the public domain might not be the latest version. Teva therefore submitted that this was an erroneous suggestion; it did not believe that prescribing information for Clenil Modulite should appear on a supplement sponsored with an unrestricted educational grant from Teva.

Teva noted that Clause 10.1 stated Promotional material and activities must not be disguised. The complainant acknowledged that the front page of the supplement clearly stated that the supplement was supported by an unrestricted educational grant from Teva. The sponsorship was therefore not disguised in any way. The supplementary information to Clause 10.1 stated when a company pays for, or otherwise secures or arranged the publication of promotional material in journals, such material must not resemble editorial matter. The supplement clearly stated the author of the material; the fact that it was a supplement produced in association with Guidelines in Practice and did not refer to it being editorial comment.

Teva further noted as recognized by the complainant, that it was stated that prescribing information could be found on the inside back page. This was included as the material had been through the Teva regulatory approval process as previously stated as was necessary with promotional material under the Code – subsequent to the supplement being written by the

author and edited by the editor of Guidelines in Practice.

In addition, the supplementary information to Clause 10.1 stated 'Sponsorship must be declared in accordance with Clause 9.10' and Clause 9.10 stated 'The declaration of sponsorship must be sufficiently prominent to ensure that readers of the sponsored material are aware of it at the outset'. Teva reiterated that the declaration of sponsorship was on the first page, and the complainant was certainly aware that this piece was sponsored by Teva UK Ltd.

With regard to the complainant's point about the inclusion of the prescribing information of Qvar and not Clenil Modulite, the Code did not call for another company's prescribing information to be provided.

Teva refuted the complainant's allegation that the supplement was 'circulated under the guise of an informed independent prescribing guideline' as the supplement clearly stated the author, the sponsor and did not refer to it being an 'independent prescribing guideline'. The supplement clearly stated that it was an article produced in association with Guidelines in Practice and written by the author. The disclaimer on the back page clearly stated The supplement has been supported by an educational grant from Teva UK Ltd. The views and opinions of contributors expressed in this publication are not necessarily those of Teva UK Ltd, the agency or of Guidelines in Practice, its publisher, advisers and advertisers. In addition, the supplement carried a job code number and a date of preparation, in line with the Code for materials that had been through Teva'a approval process.

In conclusion, Teva considered that it had complied with Clause 10.1 of the Code and that the allegations regarding bias in favour Qvar were unfounded as each section of the publication referred to Qvar and Clenil Modulite in a fair and balanced manner.

PANEL RULING

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

The supplement in question had been sponsored by Teva; the company had commissioned an agency to work with a key opinion leader to create the article. The agency had contacted the author. The article was reviewed by Teva and went through its approval process to ensure compliance with the Code. Copies were distributed as a supplement to Guidelines in Practice for which Teva had paid a fee.

The Panel considered that Teva was inextricably linked to the production of the supplement. There was no arm's length arrangement between the provision of the sponsorship and the generation of the supplement. Teva's agency and the commissioned author produced the article. The company had paid for it to be distributed. Given the company's involvement the Panel considered that the supplement was, in effect, a paid for insert which promoted Qvar.

The Panel considered that it was disguised promotion in that the insert appeared to be independent of Teva which was not so. The statement on the front cover 'Supported by an unrestricted educational grant from Teva UK Ltd' added to this impression and did not fairly reflect the actual arrangements. A breach of Clause 10.1 was ruled.

Complaint received	**18 January 2008**
Case completed	**21 February 2008**

CASE AUTH/2082/1/08

DIRECTOR, MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY and a HOSPITAL PHARMACY MANAGER v RECORDATI

Tradorec XL 'Dear Dispensary Manager' letter

The Medicines and Healthcare products Regulatory Agency (MHRA) passed to the Authority a complaint which it had received from a hospital pharmacy manager. The complaint was about a 'Dear Dispensary Manager' letter for Tradorec XL (prolonged release tramadol) dated 29 June 2007 and sent by Recordati.

As the complaint involved an alleged breach of undertaking that aspect of it was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings.

The complainant noted that the letter stated that Tradorec XL should be prescribed by brand name as 'The MHRA advises that as a Prolonged Release product, it should not be substituted with any Sustained Release or Modified Release formulation, whether branded or generic'. The complainant did not think that the MHRA had made such a statement and as far as she knew, product specificity when prescribing related to products with varying bioavailability, eg diltiazem, theophylline and in certain other situations, such as prescribing of isosorbide mononitrate XL, it was best practice to prescribe by brand but not clinically significant to do so.

In its covering letter to the Authority, the MHRA stated that it was surprised to see the complaint given the outcome of Case AUTH/2034/8/07 and it asked the Authority to investigate.

The Panel noted that Case AUTH/2034/8/07 concerned a reference in a box headed 'MHRA advice' followed by 'Prolonged Release preparations should be prescribed by brand, with no generic substitution'. Case AUTH/2034/8/07 completed on 6 September when Recordati provided an undertaking not to refer to the MHRA in its promotional material unless specifically required to do so by the licensing authority following the Panel's ruling of a breach of the Code.

The Panel noted that there were differences between the present case and Case AUTH/2034/8/07. The statement at issue was different and read 'The MHRA advises that as a Prolonged Release product, it [ie Tradorec XL] should not be substituted with any sustained Release or Modified Release formulation, whether branded or generic'. The hospital pharmacy manager's allegation that the statement was incorrect as the MHRA had made no such product specific statement had not been considered before. Recordati considered that this allegation was covered by the previous case. The Panel noted the company's submission in the previous case and comment in the Panel ruling regarding email correspondence from the MHRA. The matter was further complicated in that irrespective of the MHRA's position on this point such references could not appear in promotional material. Nonetheless, in the present case, the Panel had to rule upon the complainant's allegation on this point and considered that high standards had not been maintained. A breach of the Code was ruled.

The Panel considered that the concerns raised by the MHRA had been dealt with in the previous case. A breach of the Code was ruled.

The letter at issue in the current case was dated 29 June 2007 and the complainant thought she had received it on 5 July 2007, well ahead of the undertaking provided by Recordati in September 2007. Thus the Panel decided there was no breach of the undertaking given in the previous case, Case AUTH/2034/8/07. The Panel ruled no breach of the Code.

The Medicines and Healthcare products Regulatory Agency (MHRA) passed to the Authority a complaint which it had received from a hospital pharmacy manager. The complaint concerned a 'Dear Dispensary Manager' letter (ref TRA06-0017) for Tradorec XL (prolonged release tramadol) dated 29 June 2007 and sent by Recordati Pharmaceuticals Ltd.

As the complaint involved an alleged breach of undertaking that aspect of it was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings.

COMPLAINT

The complainant noted that the letter stated that Tradorec XL should be prescribed by brand name as 'The MHRA advises that as a Prolonged Release product, it should not be substituted with any Sustained Release or Modified Release formulation, whether branded or generic'. Recordati cited references at the end of the letter (below the prescribing information) - there was no reference 3 there - so no reference to back up its statement.

The complainant queried the claim regarding the MHRA statement as quoted above. The complainant

did not think that the MHRA had made such a statement and as far as she knew, product specificity when prescribing related to products with varying bioavailability, eg diltiazem, theophylline and in certain other situations, such as prescribing of isosorbide mononitrate XL, it was best practice to prescribe by brand but not clinically significant to do so.

In its covering letter to the Authority, the MHRA stated that it was surprised to see the complaint after the action the Authority had taken in Case AUTH/2034/8/07 and asked the Authority to investigate.

When writing to Recordati, the Authority asked it to respond in relation to Clauses 9.1 and 9.5 of the Code. The letter in question was dated 29 June 2007. If it had been sent after 6 September 2007, Recordati was also asked to respond in relation to Clauses 2 and 22 and explain the steps taken to comply with the undertaking given in relation to Case AUTH/2034/8/07.

RESPONSE

Recordati stated that the letter was sent to tell managers of dispensing practices about the Tradorec XL discount scheme.

Recordati noted that with regard to reference 3, this was included in the list of references although it was alongside reference 2, and not below it. This oversight was corrected in later versions of the prescribing information.

The reference to the MHRA in the letter was addressed in Case AUTH/2034/8/07 which concerned a leavepiece that had also referred to the MHRA. Following the Panel's ruling of a breach of the Code in that case, Recordati immediately took the steps necessary to comply with its undertaking in relation to that finding. This was not to use the leavepiece and any similar material.

Recordati noted that the complainant did not state when the material was received and as the complainant was not known to Recordati it had no way of tracing when it was sent. It appeared that the letter had either been received some months earlier or been severely delayed in the post.

With regard to Clause 9.1, Recordati believed it had maintained high standards. With regard to Clause 9.5, this had already been addressed in the earlier case and Recordati had implemented its undertaking at that time. With regard to Clauses 2 and 22, Recordati had every reason to believe that the letter was sent before 6 September 2007.

FURTHER INFORMATION FROM THE COMPLAINANT

In response to a request for further information the complainant stated that she could not recall the precise date when she received the letter at issue. Her best recollection would be 5 July 2007.

PANEL RULING

The Panel noted that the previous case, Case AUTH/2034/8/07, concerned a reference in a box headed 'MHRA advice' followed by 'Prolonged Release preparations should be prescribed by brand, with no generic substitution'. Case AUTH/2034/8/07 completed on 6 September when Recordati provided an undertaking not to refer to the MHRA in its promotional material unless specifically required to do so by the licensing authority following the Panel's ruling of a breach of the Code.

The Panel noted that there were differences between the present case and Case AUTH/2034/8/07. The statement at issue was different and read 'The MHRA advises that as a Prolonged Release product, it [ie Tradorec XL] should not be substituted with any sustained Release or Modified Release formulation, whether branded or generic'. The hospital pharmacy manager's allegation that the statement was incorrect as the MHRA had made no such product specific statement had not been considered before. Recordati considered that this allegation was covered by the previous case. The Panel noted the company's submission in the previous case and comment in the Panel ruling regarding email correspondence from the MHRA. The matter was further complicated in that irrespective of the MHRA's position on this point such references could not appear in promotional material (Clause 9.5). Nonetheless, in the present case, the Panel had to rule upon the complainant's allegation on this point and considered that high standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel considered that the concerns raised by the MHRA in relation to Clause 9.5 had been dealt with in the previous case. A breach of Clause 9.5 was ruled.

The letter at issue in the current case was dated 29 June 2007 and the complainant thought she had received it on 5 July 2007, well ahead of the undertaking provided by Recordati in September 2007. Thus the Panel decided there was no breach of the undertaking given in the previous case, Case AUTH/2034/8/07. The Panel ruled no breach of Clause 22 and hence Clauses 9.1 and 2.

Complaint received 21 January 2008

Case completed 3 March 2008

CASE AUTH/2083/1/08

GENERAL PRACTITIONER v ROCHE

Unsolicited email for Tamiflu

A general practitioner complained that Roche had sent him, via an agency, an unsolicited email about Tamiflu (oseltamivir) to his NHS email address. This was a working email address, the utility of which would be rapidly degraded by advertising or infomercial emails. The complainant stated that he had not knowingly signed up to receive any information from Roche or any other pharmaceutical company; it was most unwelcome. The ability to be able to unsubscribe did not in any way excuse the activity.

The Panel noted that the Code prohibited the use of email for promotional purposes except with the prior permission of the recipient. The Panel considered that the email on Tamiflu was clearly promotional material. Whilst it had not been sent directly by Roche, it was nonetheless an established principle under the Code that pharmaceutical companies were responsible for work undertaken by third parties on their behalf.

The Panel also noted that health professionals were told by telephone that the agency would, from time to time, send details by email about its affiliates' products and services which might include updates on specialist services, conferences and seminars, diagnostic, medical, pharmaceutical and promotional materials as well as official information. The text did not make it abundantly clear that the agency intended to send promotional material from pharmaceutical companies; the text referred to pharmaceutical *and* (emphasis added) promotional materials as if the two were wholly separate. Furthermore, the text referred to 'affiliates' of the agency. In the Panel's view pharmaceutical companies were not affiliates of the agency, and would not be seen as such. Pharmaceutical companies would be purchasing a service from the agency.

The Panel considered that the email had been unsolicited. There was no evidence to show that the complainant had given prior, fully informed, consent to receive by email promotional material from a pharmaceutical company. A breach of the Code was ruled.

A general practitioner complained about an unsolicited email about Tamiflu (oseltamivir) which he had received from Roche Products Limited via an agency.

COMPLAINT

The complainant explained that the email was sent to his NHS email address. This was a working email address, the utility of which would be rapidly degraded by advertising or infomercial emails if the industry took up this practice. The complainant stated that he had not knowingly signed up to receive any information from Roche or any other pharmaceutical company; it was most unwelcome.

The complainant submitted that if the sending of SPAM emails was not already contrary to the Code then he thought it should be. The complainant was astonished that Roche allowed its name to be associated with this behaviour as sending SPAM was associated with the seedier side of the Internet and was a practice frowned upon by most reputable organisations which wished to preserve a good name. The ability to be able to unsubscribe did not in any way excuse the activity.

When writing to Roche, the Authority asked it to respond in relation to Clause 9.9 of the Code.

RESPONSE

Roche submitted that the email was sent to provide a level of Tamiflu education to health professionals who had previously consented to receive promotional information about pharmaceutical products via email. Roche fully appreciated the requirements of the Code with regard to unsolicited communications with health professionals and therefore it was important to the company that it only sent information to individuals who had previously agreed and who would be receptive to receiving it. Roche contracted an agency that specialised in electronic communication with health professionals to facilitate this controlled distribution. Roche reviewed the agency's processes of engagement with health professionals prior to the initiation of the contract to ensure it operated within the Code, the data protection act and internal policy. Roche was therefore satisfied with the agency's level of documentation and process.

The agency was an organisation which as part of its business emailed health professionals. It conducted this work on behalf of itself and also for third parties. Roche did not commission the construction of a database as this was already in existence.

Prior to communicating with any health professional, the agency always telephoned them to explain who it was, what it did, and that in order to email them on behalf of organisations such as pharmaceutical companies, it required their email address to be provided verbally whilst on the telephone. The health professional was told that they might receive communications from one of the agency's associated companies, which would be relevant to their medical specialisation or administrative responsibilities. A transcript of the exact wording read to them over the telephone was: '[the agency] will from time to time send information by email about our affiliates'

products and services which may include updates on specialist services, conferences and seminars, diagnostic, medical, pharmaceutical and promotional materials as well as official information'.

After the telephone call the doctor then received an email (to the address they provided to the agency) confirming the points raised in the conversation and confirming an access code for NHS online directory service, an information system hosted by the agency on the Internet should they wish to visit this site. The email further explained that they would be asked to complete a short registration process if they required full access to the database provided. At this point the agency reiterated that it would send information which might include updates on specialist services, conferences and seminars, diagnostic, medical, pharmaceutical and promotional materials as well as official information, as in the transcript above. The health professional then opted in to receiving such information from the agency and further confirmed the email address to which they wished to have this information sent. If the health professional no longer wished to receive further information there was an easy opt out button available on each communication. At this point they would no longer be contacted. This ensured the agency never sent SPAM or unsolicited emails and complied with the Data Protection Act.

Roche provided copies of the promotional material information that the complainant agreed to receive via email as described in the process on 7 September 2007, and received his confirmation email to confirm his email address once more on the same day.

The complainant had received several communications since then from the agency, unrelated to Roche or any of its products. These communications had also included promotional material from other pharmaceutical companies. Therefore Roche was assured that the complainant had consented to receiving these communications and had not opted out of the system.

Roche also confirmed that the complainant did not view the material available online as there was an option allowing health professionals to choose not to. The complainant had been contacted by the agency and removed from their list of 'opted in' health professionals to ensure he did not receive further information from Roche or any other organisation including, the National Institute for Health and Clinical Excellence (NICE) and other pharmaceutical companies.

PANEL RULING

The Panel noted that Clause 9.9 prohibited the use of email for promotional purposes except with the prior permission of the recipient. The Panel considered that the email on Tamiflu was clearly promotional material. Whilst it had not been sent directly by Roche, it was nonetheless an established principle under the Code that pharmaceutical companies were responsible for work undertaken by third parties on their behalf.

The Panel also noted the script used on the telephone: health professionals were told that the agency would, from time to time, send details by email about its affiliates' products and services which might include updates on specialist services, conferences and seminars, diagnostic, medical, pharmaceutical and promotional materials as well as official information. The text did not make it abundantly clear that the company intended to send promotional material from pharmaceutical companies; the text referred to pharmaceutical *and* (emphasis added) promotional materials as if the two were wholly separate. Furthermore, the text referred to 'affiliates' of the agency. In the Panel's view pharmaceutical companies were not affiliates of the agency, and would not be seen as such. Pharmaceutical companies would be purchasing a service from the agency.

The Panel considered that the email had been unsolicited. There was no evidence to show that the complainant had given prior, fully informed, consent to receive by email promotional material from a pharmaceutical company. A breach of Clause 9.9 was ruled.

Complaint received 24 January 2008

Case completed 22 February 2008

CASE AUTH/2084/1/08 *NO BREACH OF THE CODE*

ANONYMOUS v NOVARTIS

Arrangements for a meeting and conduct of representative

An anonymous (non-contactable) complainant claimed to have been at a meeting sponsored by Novartis at which excessive hospitality had been provided and the representatives' conduct had been inappropriate.

The complainant alleged that at the meeting, held at a restaurant in January, two representatives had paid no regard to who was present; no register of attendees was kept and many of the delegates were not health professionals. There appeared to be no control of the budget and people ordered whatever food/drink they wished. The bill of approximately £2,000 for 30 people was totally unacceptable. Six doctors had take-aways of £228 on top of dining in. The two representatives who dined with the meeting also had take-aways for themselves and also took home unopened bottles of wine. One of the representatives proudly stated it was for her husband's supper. The whole evening was a gross abuse of taxpayers' money.

The Panel noted that there appeared to be a difference of opinion regarding the meeting. The complainant was anonymous and non contactable, but appeared to know enough about the meeting such as to suggest that (s)he might have been there on the night.

Novartis submitted that 42 health professionals had attended the meeting which had been held in a separate room in the restaurant, and although they had gone to the main restaurant for dinner at 9pm, the service was poor and the main course had not arrived by 10pm. Some doctors had taken their main course with them when they left.

The Panel was concerned at the arrangements. It noted that according to the agenda dinner would be served at 8.45pm. According to Novartis dinner was served at 9pm. The main course however appeared to have been seriously delayed.

The Panel was concerned that there had been a bar bill of £230.05 given that wine and water had already been provided. The Panel did not know what additional drinks had been ordered. Novartis submitted that this additional bar bill had been limited appropriately but no details were given. However according to Novartis there had been a long delay between the starter and main course in the Panel's view this might have contributed to this bill. The total cost of the meal plus drinks was £38.69 per head.

The Panel considered that the hospitality, particularly the drinks bill (£442.15), was on the outer limits of acceptability. It was concerned about the impression given by the arrangements. It was also concerned about the discrepancies between the two parties' accounts.

The Panel decided on the evidence before it that the hospitality, on balance was not unacceptable. The attendees were health professionals and the main purpose of the meeting was educational. The costs were on the limit of what health professionals would normally pay if they were paying for themselves. No breach of the Code was ruled.

COMPLAINT

The complainant alleged a waste of taxpayers' money and abuse of funding within the company. In particular the complainant noted the weekly meetings held by a named GP sponsored by the company whereby approximately one third of people attending were not from the medical profession including wives, partners, retired doctors etc. There was no control on attendance – the GP announced the next meeting weeks in advance and it was left as a free for all to attend. This was against the Code and the GP should be reprimanded and informed about the Code.

In particular the complainant noted a meeting sponsored by Novartis held at a restaurant on Thursday, 17 January. The complainant alleged that the medical representatives had paid no regard to who were present and no signatures of attendance were asked for. The complainant was not invited to sign any register and was unaware of one. The representatives appeared to have no control of the budget and people ordered whatever food/drink they wished. The total bill of approximately £2,000 was totally unacceptable regarding the reasonable refreshments interpretation of the Code. Six doctors had take-aways of £228 on top of dining in. The two representatives who dined with the meeting also ordered take-aways for themselves and had two large carrier bags waiting on the way out as well as unopened bottles of wine. One of the representatives proudly stated it was for her husband's supper. Such abuse needed reporting to Novartis for it to take action. The whole evening was a gross abuse of taxpayers' money, money that could be better spent on hip operations and such like. £2,000 spent on approximately 10 out of 30 eligible [that being a generous assessment] worked out at about £200 per head.

When writing to Novartis, the Authority asked it to respond in relation to Clauses 2, 9.1, 15.2 and 19.1 of the Code.

RESPONSE

Background to the meeting

Novartis submitted that the meeting in question was coordinated and chaired by the GP as one of a series of regular Thursday evening educational meetings. The invitation list was proposed by the GP and each invitee received an invitation outlining the programme and the location of the meeting.

The meeting was held in a private room at the restaurant starting at 7pm. Following a brief introduction by the GP, the guest speaker, a senior consultant nephrologist, spoke until 8.30pm on 'Renin Angiotensin and the Kidney: current and future therapeutic options' in the management of hypertension in the context of current BHS/NICE guidelines. Copies of the speaker's slides were provided. Following a half hour question and answer session the attendees then moved into the main restaurant for dinner at 9pm.

The meeting was coordinated by two experienced representatives both of whom had passed their ABPI examination. In addition all representatives received appropriate internal training in the management of meetings and all arrangements for this meeting, including the attendees list and meeting costs were recorded by the representatives in compliance with the company business process rules.

Registration of attendees

Novartis noted that the complainant suggested that no register of attendees was collected at the meeting, and that the associated hospitality was extended to a large number of people who were not health professionals including wives, partners and retired doctors. Neither of these assertions was true. A copy of the handwritten register from the meeting, was provided including the status of the attendees, their place of employment and signature. One of the representatives actively sought registration from attendees by circulating around the meeting room to each of the attendees. Only one attendee failed to include themselves on the register - a nursing colleague of one of the consultants attending the meeting and would be followed up with a certificate of attendance already issued and signed by the chair.

Novartis submitted that the register included 35 GPs from the local area, two consultants and three nurses. The register included several pairs of married GPs, one father and son both of whom were local health professionals and one retired GP who did locum work in the area. This was clearly at odds with the complainant's assertion that only ten of the delegates were eligible health professionals.

Provision of hospitality

Novartis submitted that the hospitality consisted of a set meal for 42, including the 40 delegates in the register plus the speaker and the attendee who as stated above was not listed in the delegate's register. The food was served as a number of dishes to be shared by each table. As a result a set meal for 42 was shared by 44 including the two representatives. Attendees were not permitted to order any additional dishes.

Each table was provided with a bottle of red wine, a bottle of white wine and a bottle of water. There was also a bar but the representatives limited this appropriately and the costs were included in the overall bill for the hospitality referred to below.

The representatives commented that service at the restaurant was poor with attendees still waiting for the main course an hour after the meal began at 9pm. As a result some of the attendees, including the speaker, who needed to leave the meeting promptly ate their starters but had food from the main course packaged to take away with them. No additional take-aways were purchased as alleged by the complainant. The representatives' report also indicated that they had underestimated the number of vegetarians at the meeting. As a result some meat dishes were left over which the representatives took away themselves rather than see wasted. Similarly one of the representatives took away one bottle of wine which was three quarters full rather than see it wasted.

Novartis submitted that the total bill for the hospitality provided for the 42 attendees plus the two representatives came to £1,702.15 (ie £38.69 per head) inclusive of dinner, drinks from the bar, pre-meeting drinks and snacks and wine and water on each table. A copy of the bill was provided.

Conclusions

Novartis did not accept the complainant's assertions of breaches of the Code in relation to the management of this meeting.

- The attendees were invited by the company and attendance was recorded. It was not 'a free for all' as suggested.
- The hospitality was clearly secondary to the scientific content of the meeting.
- All attendees were appropriate health professionals and partners and family members did not attend apart from where they where legitimate attendees in their own right.
- The hospitality was at a reasonable cost per head cost (£38.69) and no additional take-aways were purchased for attendees as alleged.
- Due to the delay in service, some attendees needed to leave the meeting promptly and so had food packed up for them to take away but this was not purchased separately.
- Any food taken from the restaurant by the representatives was leftover from the meal because of the unexpected number of vegetarians at two tables and the generous catering of the restaurant.
- Only one opened and part used bottle of wine was taken from the restaurant by a representative to avoid waste.
- Bar costs were carefully monitored by the representatives and were included in the single bill for hospitality.

Novartis did not accept that the arrangements for this meeting reflected poor standards by the company or by the representatives. Novartis also did not accept that the hospitality provided was excessive or provided to non health professionals as alleged based on the clear records maintained by the representatives. Novartis hoped that this information addressed the complainants' concerns.

FURTHER RESPONSE FROM NOVARTIS

Having given preliminary consideration to the matter, the Panel sought further information from Novartis.

Novartis reiterated that the hospitality associated with the meeting consisted of a set meal for 42 which was, shared between 44, the 42 attendees plus the two representatives.

The set meal for 42 was charged at £30 per head (including starter, main course, dessert and coffee) = £1,260.

13 bottles of house wine were charged for at £10.90 per bottle = £141.70.

21 bottles of water were charged for at £3.20 per bottle = £70.40.

Additional drinks bill = £230.05.

Total bill = £1,702.15 inclusive of service and the use of a private room.

Meeting attendees

The meeting was coordinated and chaired by a GP as one of a series of regular Thursday evening educational meetings for his local colleagues. The invitees were proposed by the GP and each received an invitation via the post outlining the programme and the location of the meeting. Further invitations were left by the representatives with practice managers to act as a reminder closer to the date of the meeting. As this was a regular programme of scientific meetings, word of mouth would have been instrumental in disseminating information about this event amongst the local healthcare community.

As demonstrated by the meeting register already provided attendees included 35 GPs, two consultants and three nurses.

PANEL RULING

The Panel noted that Clause 19 required meetings to be held in appropriate venues conducive to the main purpose of the event. Hospitality must be strictly limited to the main purpose of the event and secondary to the purpose of the meeting ie subsistence only. The level of subsistence offered must be appropriate and not out of proportion to the occasion. The cost involved must not exceed that level which the recipients would normally adopt when paying for themselves. It must not extend beyond members of the health professions or appropriate administrative staff. Spouses or partners of delegates should not be offered hospitality unless they qualified as a proper delegate or participant at the meeting in their own right.

The Panel noted that there appeared to be a difference of opinion regarding the meeting. The complainant was anonymous and non contactable, but appeared to know enough about the meeting such as to suggest that (s)he might have been there on the night.

The Panel noted Novartis' submission that 42 health professionals had attended the meeting which had been held in a separate room in the restaurant. Following the meeting the attendees had gone to the main restaurant for dinner at 9pm. The Novartis representatives stated that service was poor and the main course had not arrived by 10pm. Some doctors had taken their main course with them when they left.

The Panel was concerned at the arrangements. It noted that according to the agenda dinner would be served at 8.45pm. According to Novartis dinner was served at 9pm. The main course, however appeared to have been seriously delayed.

The Panel was concerned that there had been a bar bill of £230.05 given that wine and water had already been provided. The Panel did not know what additional drinks had been ordered. Novartis submitted that this additional bar bill had been limited appropriately but no details were given. However according to Novartis there had been a long delay between the starter and main course. In the Panel's view this might have contributed to this bill. The total cost of the meal plus drinks was £38.69 per head.

The Panel considered that the hospitality, particularly the drinks bill (£442.15), was on the outer limits of acceptability. It was concerned about the impression given by the arrangements. It was also concerned about the discrepancies between the two parties' accounts.

The Panel decided on the evidence before it that the hospitality, on balance was not unacceptable. The attendees were health professionals and the main purpose of the meeting was educational. The costs were on the limit of what health professionals would normally pay if they were paying for themselves. No breach of Clause 19.1 was ruled. The representatives had not failed to comply with the Code so no breach of Clause 15.2 was ruled. The Panel also ruled no breach of Clauses 9.1 and 2.

Complaint received	**24 January 2008**
Case completed	**26 February 2008**

CASE AUTH/2085/1/08 and AUTH/2086/1/08

MEDIA/DIRECTOR V MERCK SHARP & DOHME AND SCHERING-PLOUGH

Ezetrol insert in The Pharmaceutical Journal

A letter published in The Pharmaceutical Journal from a pharmacist at a primary care trust entitled 'Many people do not take statins as described', criticised a four page promotional insert for Ezetrol (ezetimibe) jointly sponsored by Merck Sharp & Dohme and Schering-Plough. The insert was entitled 'NICE guidance on ezetimibe: A pharmacist's perspective' and was written by a pharmacist, from an NHS Trust. Prescribing information for Ezetrol was on the back page.

The complainant was particularly critical that the insert did not refer to patient compliance with statins. The complainant also alleged that five year old data was cited in support of the claim 'Thirty five percent of patients with coronary heart disease in the UK are not reaching current government cholesterol targets despite effective treatment therapies'. The claim, however, was not supported by the data; when patients had their statin therapy reviewed then only 22% failed to reach target (Brady *et al* 2005). The complainant further noted that Brady *et al* did not state that ezetimibe had no robust cardiovascular disease outcome data, in contrast to a number of statins; something to be considered when deciding how to treat a patient who had not reached target.

In accordance with established procedures the matter was taken up by the Director as a complaint under the Code.

The Panel noted that the insert at issue was a review of the NICE guidance on ezetimibe for the treatment of primary hypercholesterolaemia. In patients with primary hypercholesterolaemia, Ezetrol was indicated for use together with a statin where the statin alone had not appropriately controlled the patient's lipid levels (Ezetrol Summary of Product Characteristics (SPC)). Given the aim of the insert and Ezetrol's licensed indication, the Panel did not consider that it was misleading not to refer to patient compliance as a reason for the failure of statin monotherapy. No breach of the Code was ruled.

The claim 'Thirty five percent of patients with coronary heart disease in the UK are not reaching current government cholesterol targets despite effective treatment therapies' which was referenced to Brady *et al* published in 2005; the companies submitted that there had not been any more recent publications in the UK. Some of the data in Brady *et al* was from May 2000. The authors set out to see whether national cholesterol targets were being met ie that statin therapy should reduce serum total cholesterol to <5mmol/L or by 25% whichever resulted in the lowest achieved level. The data showed that success in lowering cholesterol to <5mmol/L was achieved with the first dose of statin in 65% of patients and in 78% following titration or switching. It thus appeared that the 35% of patients not reaching target levels and referred to in the claim were only those who had total cholesterol of <5mmol/L on the first dose and had yet to be titrated or switched. Such additional therapy or change of therapy reduced the figure of 35% to 22%. In addition the claim did not take account of the target of reducing total cholesterol by 25%. The Panel considered that the claim was too general given the additional data; it only applied in limited circumstances. In that regard the claim was misleading, exaggerated and could not be substantiated. Breaches of the Code were ruled.

The Panel did not consider that it was misleading not to state that Ezetrol had no robust cardiovascular disease outcome data, in contrast to a number of statins. In the Panel's view readers would know the importance of lowering cholesterol and the role of surrogate markers for cardiovascular disease and that if a statin failed to bring a patient to target other therapies such as Ezetrol should be added. Ezetrol was effective in lowering surrogate markers of cardiovascular disease ie total cholesterol and LDL-cholesterol. No breach of the Code was ruled.

A letter published in The Pharmaceutical Journal from a pharmacist, at a primary care trust, entitled 'Many people do not take statins as described', criticised a four page promotional insert for Ezetrol (ezetimibe) jointly sponsored by Merck Sharp & Dohme Limited and Schering-Plough Ltd. The insert had been distributed with The Pharmaceutical Journal. The insert was entitled 'NICE guidance on ezetimibe: A pharmacist's perspective' and was written by a pharmacist, from an NHS Trust. Prescribing information for Ezetrol was on the back page.

In accordance with established procedures the matter was taken up by the Director as a complaint under the Code. The author of the letter indicated that he wanted to be involved in the complaint process.

COMPLAINT

In his letter the complainant stated that it was important that a pharmacist took the utmost care when publicly supporting an advertisement in The Pharmaceutical Journal particularly when that pharmacist was employed by the NHS to give prescribing advice. The insert advertising ezetimibe

was a case in point. No mention was made of patient compliance. In primary care it was often the case that patients' cholesterol levels were not on target because they did not take their statin as prescribed. There were many reasons for poor compliance, and primary care pharmacists were in a good position to explore these and find solutions. Similarly, community pharmacists could help with judicious use of medicines use reviews. The complainant was disappointed that the author of the insert omitted this important issue in his article.

The complainant alleged that the insert used a five-year-old survey published in the British Journal of Cardiology to support a claim that 'Thirty-five percent of patients with coronary heart disease in the UK are not reaching current government cholesterol targets despite effective treatment therapies'. There was no mention in the survey of the statin doses used except to state that the figure improved to 22% after review of statin treatment. This hardly supported the claim.

The author also did not state that ezetimibe had no robust cardiovascular disease outcome data, in contrast to a number of statins. This should be considered when deciding which path to follow when a patient was not to target.

When writing to the companies, the Authority asked them to respond in relation to Clauses 7.2, 7.4 and 7.10.

RESPONSE

Merck Sharp & Dohme and Schering-Plough stated that the purpose of the insert in The Pharmaceutical Journal was to alert its readers to the recent NICE guidance about ezetimibe which was published on the NICE website in September 2007. The insert was structured as follows:

- Page 1 - provided an introductory overview of the whole NICE guidance from a pharmacist's perspective;
- Page 2 - gave a succinct, fair and balanced summary of the 31 page NICE guidance on ezetimibe so that the key conclusions with respect to its recommended use in the NHS in terms of clinical and cost-effectiveness were accurately portrayed in a readily assimilated form;
- Page 3 - depicted how this new guidance might be applied in routine clinical practice and in accordance with previous NICE guidance on statins by providing a hypothetical example of the treatment options available for suitable patients. The 40mg dose of simvastatin was chosen for the treatment algorithm as this was now the most widely prescribed dose;
- Page 4 - included the requisite prescribing information.

Patient compliance

a) Title of the letter

The companies noted that the title of the letter, 'Many people do not take statins as described', indicated the key issue that the author wished to draw the readers' attention was patient compliance (see also comments below). Whereas the NICE guidance for ezetimibe referred to statins, this was only in the context of its two main indications being either monotherapy, when patients were unable to tolerate statins or they were contraindicated, or as combination therapy when additional efficacy in cholesterol lowering was required.

The companies submitted that statins per se, were not the focus of the NICE guidance at issue; the guidance did not refer to statin compliance. The nature and purpose of the insert was made clear throughout. At the top of the first page in large, bold type and capital letters was the heading 'NICE GUIDANCE ON EZETIMIBE:' The second page of the insert similarly had the large heading 'NICE GUIDANCE – SUMMARY' clearly displayed. Consequently the reader was left in no doubt as to what the insert related, namely the guidance issued by NICE. The insert was not intended to provide a complete overview of all aspects of the management of patients with hypercholesterolaemia. Nonetheless, the author stated in the third paragraph what was current practice in the UK, until the introduction of this new guidance, as follows 'Current prescribing practice if a patient's cholesterol is not managed to government recommended targets of 5mmol/l for total cholesterol (TC) and 3mmol/l for a low density lipoprotein cholesterol (LDL-C) is to up-titrate a generic statin dose, or to switch to an alternative branded statin.'

b) No mention was made of patient compliance

The companies acknowledged that patient compliance could be a major issue for prescribed medicines and pharmacists would wish to ensure they were appropriately used so as to maximise the benefit they might provide and lessen the chances of unwanted side effects. However, the purpose of the insert was to summarise the NICE guidance on ezetimibe, which did not refer to patient compliance and statins. Hence it was not included.

c) No mention was made of the role of primary care pharmacists in exploring the reason for poor compliance (of statins) and finding solutions

The companies submitted that strategies to improve compliance of cholesterol lowering agents would be welcomed, however, this was not addressed in the NICE guidance for ezetimibe. These issues were, however, referred to in the second paragraph of the insert where the author stated 'The NICE guidance is of particular interest to pharmacists as it applies directly to our daily work in providing prescribing guidance on cholesterol management'. It was also referred to in paragraph 3, where he stated that pharmacists looked at a variety of factors before prescribing or providing guidance on lipid lowering management, including the efficacy, tolerability and cost of a treatment.

The companies submitted that whilst the appropriate

use of statins and patient compliance was undoubtedly an important feature in general practice, (and indeed a constant challenge for all medicines administered for chronic and largely asymptomatic medical conditions), it was neither referred to in the NICE guidance for ezetimibe nor in the Ezetrol summary of product characteristics (SPC). Consequently it was not referred to in the insert as it was something all pharmacists should take heed of in relation to all medicines.

The suggestion that the author, a pharmacist employed by the NHS to give prescribing advice, might not have taken utmost care when supporting the insert

The companies submitted that the author was chosen to provide his personal perspective on the NICE guidance. He had sufficient experience to comment on this issue as he was a prescribing consultant pharmacist to primary care and was currently involved in nurse prescribing and the British Heart Foundation at national level-qualifications, which indicated that he was intimately involved in this therapeutic area. His personal perspective represented his independent and sincerely held beliefs on the matter and the insert was reviewed by certified signatories, for compliance with the Code rather than challenging certain non-specific factors that pharmacists should take into account when advising patients on their medicines, such as patient compliance. Declarations and sponsorship were prominently declared.

The insert used a 5 year old survey published in the British Journal of Cardiology to support its claim that thirty-five percent of patients with coronary heart disease in the UK were not reaching targets despite effective treatments

Brady *et al* (2005) had been used to support this claim. The full reference for this publication was given on the last page of the insert. The complainant was therefore wrong to state that the survey was five years old. In addition it was a highly appropriate reference to use as it was drawn from the MediPlus database, run by IMS, involved 8,434 subjects and was published in a peer-reviewed journal by a consultant cardiologist.

The companies submitted that as the insert was prepared in December 2007, it was entirely in keeping to use a paper which was only 2 years old. Nonetheless, the companies had searched Medline search using 'statin prescribing in the UK' and 'achievement of cholesterol targets' to see if there had been any more recent publications in the UK and none were found. Thus Brady *et al* was the most up-to-date and current data in the public domain.

The claim that 35% of patients with coronary heart disease in the UK were not reaching current government targets despite effective treatment therapies was from Brady *et al* which showed that for all 8,434 subjects analysed in the survey only 5,516 (65.4%) achieved a target reduction of < 5mmol/l. The paper also displayed various different treatment scenarios with the accompanying target attainment. Rather than being selective in using these different sub groups, it was more representative to use the figure given for the whole database, as this was more likely to reflect current practice and thus the reality of statin prescribing in primary care. The complainant was therefore incorrect in assuming that the 35% related to target attainment when initiating statin therapy.

The use of such a population-based approach was in line with that taken by NICE, which considered target attainment in the patient population as a whole, and not certain sub segments. This was borne out by the NICE guidance for ezetimibe which stated that 'In England, the average total cholesterol concentration in adults is approximately 5.6 mmol/litre' (Brady *et al*). Clearly this indicated that for the population as a whole, 50% of people had cholesterol values > 5 mmol/l which would more than adequately support the assumption from the MediPlus database that 35% of patients with CHD had cholesterol values > 5 mmol/l.

There was no mention of the statin doses used except to say that the figure improved to 22% after review of statin treatment

The companies submitted that although Brady *et al* did not mention specific doses for the statins, it further sub divided the results according to whether patients were on their initial statin dose, titrated once, twice or more, titrated and switched, switched not titrated or any titration and switch, so there were plenty of ways that the data could be analysed according to the different management paths taken.

The achievement of the target attainment of <5 mmol/l for patients who had both a titration and switch was 78%. However this was only achieved in 1,478 subjects (17.5%) and so this neither reflected common practice nor the reality of statin prescribing in the UK.

The author of the insert also omitted to state that ezetimibe had no robust cardiovascular disease outcome data, in contrast to a number of statins. This should be taken into account when deciding which path to follow when a patient was not at target

The companies submitted that section 4.1.1 of the NICE guidance for ezetimibe briefly referred to the lack of any outcome studies but the appraisal committee dismissed this in terms of its assessment of clinical outcomes as follows; 'No studies reported health-related quality of life or clinical end points such as cardiovascular morbidity and mortality; in the trials identified, surrogate outcomes such as total cholesterol, LDL cholesterol, HDL cholesterol and TG concentrations were used as indicators of clinical outcomes'. Section 4.3.5 also stated that 'The Committee agreed that there is sufficient evidence to link reductions in LDL cholesterol concentrations induced by treatment with ezetimibe with future reductions in cardiovascular events'.

In a summary review of the NICE guidance for ezetimibe the companies submitted that it would be inappropriate to make comparisons with the statins which were outside the scope of the review.

Page 3 of the insert depicted a hypothetical treatment algorithm which reflected common UK practice, the NICE guidance for the use of statins and Section 4.3.11 of the NICE guidance for ezetimibe which stated that 'The Committee agreed that therefore adding ezetimibe to initial statin therapy as a treatment option is a cost effective use of NHS resources when compared with switching to an alternative statin'.

In conclusion the companies submitted that although the complainant made some valid points regarding patient compliance and the role that primary care pharmacists might be able to play, these issues should be debated among pharmacists. The insert accurately reflected the NICE guidance on ezetimibe and so was accurate, balanced, fair, objective, unambiguous, based on an up-to-date evaluation of all the evidence, substantiable and promoted the rationale use of medicines in line with NICE guidance. The companies therefore refuted the alleged breaches of Clauses 7.2, 7.4 and 7.10 of the Code.

PANEL RULING

The Panel noted that the insert at issue was a review of the NICE guidance on ezetimibe (Ezetrol) for the treatment of primary hypercholesterolaemia. In patients with primary hypercholesterolaemia, Ezetrol was indicated for use together with a statin where the statin alone had not appropriately controlled the patient's lipid levels (Ezetrol SPC). Given the aim of the insert and Ezetrol's licensed indication, the Panel did not consider that it was misleading not to refer to patient compliance as a reason for the failure of statin monotherapy. No breach of Clause 7.2 was ruled.

The Panel noted that page 3 of the insert included the claim 'Thirty five percent of patients with coronary heart disease in the UK are not reaching current government cholesterol targets despite effective treatment therapies' which was referenced to Brady *et al*. Brady *et al* was published in 2005; the companies submitted that there had not been any more recent publications in the UK. Brady *et al* was in two parts. Firstly, Mediplus prescribing database of 80,000 patients with established CHD of which 8434 were on a statin, sampled from May 2000. This data was examined up until December 2002 before the availability of rosuvastatin or ezetimibe to see where cholesterol targets were met at that time and to determine prescribing patterns. Secondly, in January 2003 a postal survey of GPs who had contributed to the Mediplus database. The dual surveys were to show the difference between expectation and actual achievement in statin prescribing in the UK general practice. The authors set out to see whether national cholesterol targets were being met ie that statin therapy should reduce serum total cholesterol to <5mmol/L or by 25% whichever resulted in the lowest achieved level. The data showed that success in lowering cholesterol to <5mmol/L was achieved with the first dose of statin in 65% of patients and in 78% following titration or switching. It thus appeared that the 35% of patients not reaching target levels and referred to in the claim were only those who had total cholesterol of <5mmol/L on the first dose and had yet to be titrated or switched. Such additional therapy or change of therapy reduced the figure of 35% to 22%. In addition the claim did not take account of the target of reducing total cholesterol by 25%. The Panel considered that the claim was too general given the additional data; it only applied in limited circumstances. In that regard the claim was misleading, exaggerated and could not be substantiated. Breaches of Clauses 7.2, 7.4 and 7.10 were ruled.

The Panel did not consider that it was misleading not to state that Ezetrol had no robust cardiovascular disease outcome data, in contrast to a number of statins. In the Panel's view readers would know the importance of lowering cholesterol and the role of surrogate markers for cardiovascular disease and that if a statin failed to bring a patient to target other therapies such as Ezetrol should be added. Ezetrol was effective in lowering surrogate markers of cardiovascular disease ie total cholesterol and LDL-cholesterol. The Panel did not consider that the insert was misleading with regard to the failure to mention that Ezetrol had no cardiovascular disease outcome data. No breach of Clauses 7.2, 7.4 and 7.10 was ruled.

Proceedings commenced	**25 January 2008**
Cases completed	**10 March 2008**

CASE AUTH/2087/1/08

UCB PHARMA v FLYNN PHARMA

Medikinet XL 'Dear Doctor' letter

UCB Pharma complained about a 'Dear Doctor' promotional letter sent by Flynn Pharma in response to a supply problem with UCB's product Equasym (methylphenidate immediate release). The letter promoted Flynn's product Medikinet XL (methylphenidate modified release). UCB alleged that promoting medicines in such a way did not maintain high standards in breach of the Code.

Readers were told that to alleviate the supply problems with [Equasym] Flynn was trying to increase its supply of immediate release methylphenidate. The letter also stated that 'Medikinet XL is the only sustained release methylphenidate available in the UK which is a direct replacement for a b.d. dosage of immediate release methylphenidate'. UCB alleged that this claim could not be substantiated.

The Panel did not consider that issuing a letter referring to supply problems of a competitor product was necessarily a breach of the Code. There had been supply problems with UCB's product, Equasym when the letter was sent. The Panel did not consider that promoting in this way meant that high standards had not been maintained as alleged and no breach of the Code was ruled.

With regard to the claim 'Medikinet XL is the only sustained release methylphenidate available in the UK which is a direct replacement for a b.d. dosage of immediate release methylphenidate', the Panel noted that the Equasym XL Summary of Product Characteristics (SPC) stated that patients established on an immediate release methylphenidate formulation might be switched to the milligram equivalent daily dose of Equasym XL. The claim at issue was thus misleading; Medikinet XL was not the only sustained release methylphenidate available as a direct replacement for bd dosage of immediate release methylphenidate. Equasym XL could also be used. A breach of the Code was ruled.

UCB Pharma Ltd explained that manufacturing issues had led to a temporary supply shortage of Equasym (methylphenidate immediate release) tablets. The supply issue occurred in November 2007 and was resolved by 14 December 2007. UCB had managed the issue according to the Department of Health (DoH) and the Association of the British Pharmaceutical Industry (ABPI) Best Practice Guidance 'Notification and Management of Medicines Shortages' (January 2007), and had contacted the DoH as part of the process.

UCB complained about a 'Dear Doctor' promotional letter sent by Flynn Pharma Ltd in response to the supply problem with Equasym. The letter had been sent on 18 November 2007 to paediatricians and child psychiatrists and was headed 'Shortage of methylphenidate immediate release tablets'. Readers were told that there were supply problems with the leading brand of immediate release methylphenidate (UCB's Equasym) and that to alleviate the problem Flynn was attempting to increase supply of its immediate release methylphenidate tablets, Medikinet. The letter also stated that 'Medikinet XL is the only sustained release methylphenidate available in the UK which is a direct replacement for a b.d. dosage of immediate release methylphenidate'.

UCB supplied Equasym XL (modified release methylphenidate). Methylphenidate, immediate or controlled release, was used as part of a comprehensive treatment plan in attention deficit/hyperactivity disorder (ADHD) in children over six when remedial measures alone proved insufficient.

COMPLAINT

UCB stated that the letter came to its attention when it started receiving telephone calls from representatives and health professionals. The letter was sent to approximately 3,000 paediatricians and 800 child psychiatrists on 18 November 2007 and Flynn health specialists were also provided with a copy. The letter referred to a shortage of the leading brand of methylphenidate immediate release tablets which, as conceded by Flynn, was immediately identifiable as Equasym.

UCB understood that the DoH asked Flynn whether production of its immediate release methylphenidate tablet (Medikinet) could be increased. UCB believed that this discussion with the DoH resulted in the production of the 'Dear Doctor' letter. UCB alleged that promoting medicines in such a way was not maintaining high standards and in breach of Clause 9.1 of the Code.

With regard to the claim that 'Medikinet XL is the only sustained release methylphenidate available in the UK which is a direct replacement for a b.d. dosage of immediate release methylphenidate', the Equasym XL summary of product characteristics (SPC), Section 4.2 stated that individuals might be switched directly from immediate release methylphenidate to Equasym XL, or be started on Equasym XL as a direct alternative to methylphenidate immediate release. UCB alleged that the Equasym XL SPC demonstrated that the claim was not substantiable, in breach of Clause 7.2 of the Code.

RESPONSE

Flynn submitted that the background context and stimulus to issue the letter was the supply of methylphenidate tablets (immediate release) in the UK. The product was available in 5mg, 10mg and 20mg, although in the case of the 5mg and 20mg Flynn and UCB were the only two suppliers. Flynn as a relatively recent market entrant (March 2007), supplied only a small proportion of the market. In contrast, UCB as the established player supplied an estimated 80% of demand for the 5mg and 20mg strengths and approximately 25% of demand for the 10mg strength where other suppliers also competed. Thus one could readily predict that any interruption in supply from the dominant supplier had every potential to impact on patient care. Without responsible communications, it was also improbable that a second minority supplier would be able to maintain continuity of supply for anything other than a very short period before its own supplies were exhausted.

Flynn submitted that these products were used in sensitive and vulnerable patients ie, juveniles and adolescents with ADHD. Further, the numbers of patients potentially affected were not trivial. Prescribing and Cost Analysis data for 2006 indicated a total of around 50,000 prescriptions for the 5mg strength and 7,000 for the 20mg strength in 2006 in the retail sector (primary healthcare). On a simple pro rata basis, this equated to about 1,000 scripts/patients per week for the 5mg and about 135 scripts/patients per week for the 20mg strength. Although more than 90% of supply occurred in primary care, the diagnosis and prescription (or revision/change of prescription) of medicine for ADHD occurred exclusively in primary (sic) care (hospital environment) through child psychiatrists and paediatricians with relevant experience.

Thus Flynn submitted that it had acted properly and responsibly in issuing the letter to clinicians in primary care. It was issued because of an interruption in supply by UCB, which prescribers and suppliers were not told about. From late October 2007 Flynn received calls and contacts from wholesalers, pharmacists and doctors who thought that methylphenidate (immediate release) was out of stock. In other words, they thought that none was available, and by inference, that both UCB and Flynn could not supply. This was not so.

Further, from 1 October 2007 for a period of 2 years, Flynn was awarded the national contract to supply hospitals in England with all of their methylphenidate immediate release 5mg, 10mg and 20mg. In other words, all requirements for these products in NHS hospitals in England should be met with the supply of Medikinet XL until September 2009 or some 22 months after the letter was issued. The substantial majority of the recipients of the letter in question were the prescribers in those hospitals and if copies of the letter still existed or were in circulation, they should not impact the prescribing practice of those particular doctors

Flynn alleged that UCB's communications had to date been ambiguous and incomplete as to the nature and extent of the shortage. UCB's letter of 30 November referred to 'potential shortages'. To be clear – this was approximately one month after Flynn had become aware of 'actual shortages'. UCB's letter of 20 December stated that 'the stock shortage….was a temporary one which has been completely resolved'. UCB's subsequent complaint to the Authority was more specific in stating 'The issue was resolved by 14 December 2007'. As of 8 February 2008, Flynn was still not confident that this was so. Flynn was advised by two of the main three wholesalers in the UK that Equasym 20mg continued to be unavailable. Flynn provided a recent out of stock report for one of the wholesalers as confirmation which implied a date of March (2008) for resolution of the problem. A significant percentage of pharmacists relied on either of the two wholesalers and therefore Flynn could not reconcile a statement that the situation was 'fully resolved' with this position.

The alleged breach of Clause 9.1 was a statement of opinion and was not supported by evidence or reasoned argument. Further the alleged breach of Clause 9.1 was a misapplication of both the letter and intent of that particular clause, which it understood was concerned primarily with matters of suitability and taste and the special nature of medicines. The letter itself might be considered in two parts – the first was a factual (trade) announcement as to the availability of methylphenidate immediate release tablets. That it did not mention Equasym by name was irrelevant, since the Code did not prohibit the use of competitor brand names. The second part of the letter referred to an 'alternative solution' (to the supply problem), offered by Medikinet XL, Flynn's modified release methylphenidate. This made a promotional claim and hence the use of an appropriate reference and prescribing information. The claim itself was subject to a separate allegation. If, however, the essence of UCB's concern was that it was inappropriate to mix statements of fact or trade announcements (eg pricing and availability information), with promotion, then it should state that. Regardless, it was Flynn's view that such practice was permissible, proper and consistent with the advertising and promotion of medicines in the UK for many years.

Flynn submitted that if however, UCB's concern was that it was not the responsibility of a company to communicate shortages or situations that might and did impact on markets in which it operated, then again it failed to see the reasoning behind this. The fact that a competitor took issue to such a situation being communicated was quite simply, not in breach of the Code. Nor, did the letter offend against the generally held standards and norms in pharmaceutical promotion; to state that a product was unavailable was as permissible as it was to make comparative claims of a clinical or pharmaceutical nature. Finally, the shortage itself was not disputed – in other words, there was a shortage, and indeed questions remained as to the

availability of the 20mg tablets.

With regard to the claim 'Medikinet XL is the only sustained release methylphenidate available in the UK which is a direct replacement for a b.d. dosage of immediate release methylphenidate' Flynn that SPCs were carefully crafted and important documents, the wording of which was assessed in detail and approved by the Medicines and Healthcare products Regulatory Agency (MHRA). It was appropriate therefore to refer to the precise language of this document. The Equasym XL SPC in Section 4.2 stated that, 'For example, 20mg of Equasym XL is intended to take the place of 10mg at breakfast and 10mg at lunchtime' and that 'Equasym XL 10mg once daily may be used in place of immediate release methylphenidate hydrochloride 5mg twice daily from the beginning of treatment …' UCB's use of the highlighted wording in its complaint was at variance with the SPC itself, and conveyed a degree of certainty not supported by the language therein. In Flynn's view, the SPC fell short of substantiating a claim that Equasym XL was a **direct** replacement for immediate release methylphenidate.

Flynn submitted that the equivalence of immediate release products and their modified release counterparts was frequently debated. Whereas in some instances, different brands of a modified release medicine were considered interchangeable (or direct replacements) with each other and their immediate release equivalents, methylphenidate was not one of them.

Flynn submitted that there was a clear and direct relationship between the pharmacokinetic and pharmacodynamic (clinical) response, such that formulation and release profile very much mattered. Indeed, the authoritative expert comment on the subject might be found in 'Long-acting medications for the hyperkinetic disorders – A systematic review and European treatment guideline' (Banaschewski *et al* 2006), which in reference to modified release products stated, 'all provide a mixture of immediate- and extended-release methylphenidate; they differ in the physics of the delayed release system and in the proportion of immediate to delayed'. It was this variation in the release profiles of the competing brands of modified release methylphenidate that demanded prescription by brand and in practice, the selection of different brands to suit individual patients. The clinical profile of the underlying hyperkinetic disorder and inter-subject variability was such that different patients exhibited symptoms to a greater or lesser degree in the morning or afternoon. Thus it was clinically useful and prudent when selecting and prescribing a modified release methylphenidate product, to select one with a release profile that matched the particular patient's underlying hyperkinetic profile. All brands were different and all had a place. Another common feature in clinical practice was the use of early morning/late afternoon, early evening 'top-up' doses to add-on to the release profile offered by a specific product. In regard to Equasym XL the same review stated that '30% of the dose is provided by the immediate release component and 70% of the dose is provided by the delayed release component'.

In relation to Medikinet XL, the European guideline stated '50% immediate with 50% extended'. Both Equasym XL and Medikinet XL were designed to release methylphenidate over an approximately 8 hour period, whereas the immediate release presentations provided release and clinical effect over an approximate 4 hour period.

Medikinet XL was the only modified release presentation that had been shown to be bioequivalent to a bd dosage (Döpfner *et al* 2003) cited in the letter at issue. That is to say, a single dose of Medikinet XL would produce plasma levels of methylphenidate equivalent to half the same mg dose taken twice daily (with a dosing interval of approximately four hours). Medikinet XL had also been shown to be clinically equivalent (Döpfner *et al* 2004). The same could not be said of Equasym XL.

The claim asserted that Medikinet XL was the only direct replacement for a bd dosage. In other words for example, that a dose of Medikinet XL 10mg once daily was the only direct replacement for a dosage of 5mg immediate release bd. Put simply, Flynn was stating that '5 + 5 = 10'. The essence of UCB's implied claim was that '3 + 7 = 10'. However, '5 + 5' was not the same as '3 + 7' – the two modified release products produced different pharmacokinetic and pharmacodynamic profiles and were not interchangeable or equivalent. For UCB's argument to hold true, namely that Equasym XL was also a direct replacement, would then suggest the contrary and that by inference, one (modified release) product could be substituted for the other. Flynn cited Döpfner *et al*, (2003), a bioequivalency study. To support the statement of clinical equivalence Flynn noted that Döpfner *et al*, (2004) reported a comparative efficacy of once-a-day extended release (Medikinet XL), twice-daily immediate-release methylphenidate, and placebo. This was a randomised double-blind crossover study with assessments of clinical response obtained five times over an eight hour period. This study provided robust evidence of the clinical equivalence of Medikinet XL and immediate release methylphenidate at daily dosages of 5mg, 10mg, 15mg and 20mg. On the basis of the above Flynn submitted that there was no breach of Clause 7.2.

PANEL RULING

The Panel did not consider that issuing a letter referring to supply problems of a competitor product was necessarily a breach of the Code. There had been supply problems with UCB's product, Equasym when the letter had been sent. It stated that the leading brand might not be available for patients and offered two solutions, these being increasing supply of Medikinet or using Medikinet XL. The Panel did not consider that promoting in this way meant that high standards had not been maintained as alleged and no breach of Clause 9.1 was ruled.

With regard to the claim 'Medikinet XL is the only sustained release methylphenidate available in the UK which is a direct replacement for a bd dosage of immediate release methylphenidate', the Panel examined the Equasym XL SPC. Section 4.2, in a reference to patients currently using methylphenidate, stated that patients established on an immediate release methylphenidate formulation might be switched to the milligram equivalent daily dose of Equasym XL. A comparable statement appeared in the Medikinet XL SPC. The Panel considered that the claim at issue was misleading given the statements in the Equasym XL SPC.

Medikinet XL was not the only sustained release methylphenidate available as a direct replacement for bd dosage of immediate release methylphenidate. Equasym XL could also be used. The Panel did not consider that the claim related to changing from one modified release product to another as appeared to be implied from much of Flynn's response to this point. The Panel ruled a breach of Clause 7.2.

Complaint received **25 January 2008**

Case completed **4 March 2008**

CASE AUTH/2088/1/08

GENERAL PRACTITIONER v ASTRAZENECA

Unsolicited email about Crestor

A general practitioner complained that AstraZeneca had sent him, via an agency, an unsolicited email about Crestor (rosuvastatin) to his NHS email address. This was a working email address, the utility of which would be rapidly degraded by advertising or infomercial emails. The complainant stated that he had not knowingly signed up to receive any information from AstraZeneca or any other pharmaceutical company; it was most unwelcome. The ability to be able to unsubscribe did not in any way excuse the activity.

The Panel noted that the Code prohibited the use of email for promotional purposes except with the prior permission of the recipient. The Panel considered that the email on Crestor was clearly promotional material. Whilst it had not been sent directly by AstraZeneca, it was nonetheless an established principle under the Code that pharmaceutical companies were responsible for work undertaken by third parties on their behalf.

The Panel also noted that health professionals were told by telephone that the agency would, from time to time, send information by email about its affiliates' products and services which might include updates on specialist services, conferences and seminars, diagnostic, medical, pharmaceutical and promotional materials as well as official information. The text did not make it abundantly clear that the agency intended to send promotional material from pharmaceutical companies; the text referred to pharmaceutical *and* (emphasis added) promotional materials as if the two were wholly separate. Furthermore, the text referred to 'affiliates' of the agency. In the Panel's view pharmaceutical companies were not affiliates of the agency, and would not be seen as such. Pharmaceutical companies would be purchasing a service from the agency. Similar text appeared in the subsequent confirmatory email.

The Panel considered that the email had been unsolicited. There was no evidence to show that the complainant had given prior, fully informed consent to receive by email promotional material from a pharmaceutical company. A breach of the Code was ruled.

A general practitioner complained about an unsolicited email about Crestor (rosuvastatin) received from AstraZeneca UK.

COMPLAINT

The complainant explained that the email was sent to his NHS email address. This was a working email address, the utility of which would be rapidly degraded by advertising or infomercial emails if the industry took up this practice. The complainant stated that he had not knowingly signed up to receive any information from AstraZeneca or any other pharmaceutical company; it was most unwelcome.

The complainant submitted that if the sending of SPAM emails was not already contrary to the Code then he thought it should be. The complainant was astonished that AstraZeneca allowed its name to be associated with this behaviour as sending SPAM was associated with the seedier side of the Internet and was a practice frowned upon by most reputable organisations which wished to preserve a good name. The ability to be able to unsubscribe did not in any way excuse the activity.

When writing to AstraZeneca, the Authority asked it to respond to Clause 9.9 of the Code.

RESPONSE

AstraZeneca submitted that it had commissioned an agency to distribute an educational email on hyperlipidaemia to primary care physicians who had subscribed to the agency's services. The agency sent regular emails containing information on products and services on behalf of several government bodies and the pharmaceutical industry. The commission by AstraZeneca was a one-off agreement and there were no additional plans to re-send the material.

AstraZeneca submitted that the agency operated an opt-in process for receipt of email. Health professionals were initially telephoned by the agency which outlined who it was, what it did and the services offered, explaining that from time to time it might send emails about affiliated products and services including pharmaceutical promotional material.

The agency asked if the health professional was interested in receiving this service. If so they were asked to provide their email address.

The agency then sent a confirmatory email containing the health professional's unique access code in order to access the website. This email reiterated the information given in the initial telephone call and specifically highlighted that the agency would send 'from time to time information by email about our affiliates' products and services which may include updates on specialist services, conferences and seminars, diagnostic, medical, pharmaceutical and promotional materials as well as official information'. The health professional was then required to log in and enter their contact details, before the service was finally activated.

AstraZeneca had confirmed the process with the

agency before approving the material in question, and was assured that the material would be sent to 18,000 GPs who had opted-in to the service. This service also offered an opt-out facility to allow those who no longer wished to receive such material to be removed from the subscribing list. This facility was on the front page of the material. A copy of a letter from the agency describing the validation process and services was provided together with the telephone transcript and the confirmation email. According to the agency, the complainant was initially contacted in September 2007, at which time he confirmed his contact information, including his email address, and subsequently received a follow-up confirmatory email as outlined above. He had been included in a number of communications from the agency since September 2007.

In summary, AstraZeneca submitted that it was satisfied that the process and procedures as described above were in accordance with both the letter and the spirit of the Code and that the email distribution was from a genuine, validated, opt-in database.

AstraZeneca understood the complainant's frustration and annoyance on receiving this email. Nevertheless on this particular occasion AstraZeneca did not believe that this was an unsolicited email.

PANEL MINUTE

The Panel noted that Clause 9.9 prohibited the use of email for promotional purposes except with the prior permission of the recipient. The Panel considered that the email on Crestor was clearly promotional material. Whilst it had not been sent directly by AstraZeneca, it was nonetheless an established principle under the Code that pharmaceutical companies were responsible for work undertaken by third parties on their behalf.

The Panel also noted the script used on the telephone: health professionals were told that the agency would, from time to time, send information by email about its affiliates' products and services which might include updates on specialist services, conferences and seminars, diagnostic, medical, pharmaceutical and promotional materials as well as official information. The text did not make it abundantly clear that the agency intended to send promotional material from pharmaceutical companies; the text referred to pharmaceutical *and* (emphasis added) promotional materials as if the two were wholly separate. Furthermore, the text referred to 'affiliates' of the agency. In the Panel's view pharmaceutical companies were not affiliates of the agency, and would not be seen as such. Pharmaceutical companies would be purchasing a service from the agency. Similar text appeared in the subsequent confirmatory email.

The Panel considered that the email had been unsolicited. There was no evidence to show that the complainant had given prior, fully informed, consent to receive by email promotional material from a pharmaceutical company. A breach of Clause 9.9 was ruled.

Complaint received	25 January 2008
Case completed	29 February 2008

BAYER SCHERING PHARMA v LILLY

Alleged promotion of unlicensed indication

Bayer Schering Pharma complained about the possible promotion by Lilly of Cialis (tadalafil) of an unlicensed indication based on market research monitoring reports.

Bayer Schering alleged, inter alia, that the promotion of an unlicensed indication and an unlicensed dosage brought discredit to and reduced confidence in the industry in breach of Clause 2; it was misleading to imply that an unlicensed indication was consistent with the summary of product characteristics (SPC) and Lilly's refusal to supply information as requested and to regard the matter as closed without discussing conciliation was not consistent with maintaining high standards.

The Panel noted that the sole evidence provided by Bayer Schering comprised detail recall data from a small number of doctors. Three separate entries referred to Cialis and its cardiovascular effect. The Panel noted Lilly's submission about the survey's methodology and weight to be attached to such evidence.

The Panel accepted that it was difficult to know precisely what representatives were saying to health professionals. This was one reason why the Code required briefing material to be prepared.

The promotional and briefing materials provided neither referred to a possibility that Cialis had a positive cardiovascular effect nor to doses other than 10mg and 20mg. The Panel was nonetheless concerned that physicians recalled that smaller doses of Cialis were protective but did not consider that this was consistent with the material provided by Lilly.

The Panel noted that Bayer Schering had to establish its case on the balance of probabilities. Bayer Schering had referred to the '*possibility* that Cialis had been, and was being, promoted outside its licence in relation to cardiovascular conditions' (emphasis added). The Panel considered that Bayer Schering had not provided sufficient evidence to establish that, on the balance of probabilities, this was so. The Panel ruled no breach of the Code.

With regard to the alleged breach in relation to Lilly's refusal to supply information as requested or discuss conciliation, the Panel considered that there was no breach. There was no obligation for companies to discuss conciliation. There was only a requirement for the complainant to attempt inter-company dialogue prior to submitting a complaint to the Authority.

Bayer Schering Pharma complained about the promotion of Cialis (tadalafil) by Eli Lilly and Company Limited. Bayer Schering supplied Levitra (vardenafil).

COMPLAINT

Bayer Schering's principal concern was the possible promotion of Cialis for an unlicensed indication based on market research agency monitoring reports (provided) for March and September 2007 which indicated the possibility that Cialis had been (and was being) promoted in relation to cardiovascular conditions. Bayer Schering had asked Lilly to provide briefing materials for its representatives and speakers so that it could rule out Lilly's direct or indirect involvement in such practice. Unfortunately Lilly rejected inter-company correspondence on this matter and left Bayer Schering in a position unable to continue inter-company dialogue directed at assessing and resolving this matter. Since then Bayer Schering had received a further detail recall from December 2007 (provided). This appeared to indicate a continuance of the recall pattern evidenced by the earlier monitoring. In view of the documented recall pattern of health professionals referring to the use of Cialis for an unlicensed indication Bayer Schering alleged this matter might potentially be serious and should not be ignored, however, as a consequence of Lilly's refusal to engage it could not investigate this matter any further through its preferred route of inter-company dialogue. In the circumstances Bayer Schering referred the matter to the Authority.

Bayer Schering alleged breaches of:

Clause 3.2, promoting a medicine within [sic] the terms of its marketing authorization;
Clause 2, promotion of an unlicensed indication and an unlicensed dosage brought discredit to and reduced confidence in the industry;
Clause 7.2, it was misleading to imply by promotion that an unlicensed indication was consistent with the summary of product characteristics (SPC) and
Clause 9.1, Lilly's refusal to supply information as requested and to regard the matter as closed without discussing conciliation was not consistent with maintaining high standards.

RESPONSE

Lilly strenuously denied the allegation and remained confident that representatives had not promoted Cialis outside of the product licence, as set out in inter-company correspondence dated 13 December. This was supported by a number of factors. Firstly, all material used by representatives was certified in accordance with the Code. Secondly, all representatives' training material was certified as per Clause 15.9, and thirdly,

all slide presentations at Lilly promotional meetings produced by external speakers were reviewed for medical accuracy.

Lilly provided a summary of all relevant Cialis promotional material from 2007, an explanation of how it was used and associated briefing documents. Lilly considered several of these items, specifically the Cialis detail aids, objection handlers and associated briefing material to be company proprietary and hence company confidential. These materials were not left with physicians and therefore not used independently of the representative. Lilly requested that all material remained confidential and not be disclosed to Bayer Schering. The sharing of any material would provide Bayer Schering with commercial information which was beyond that necessary to resolve the complaint.

Lilly stated that the basis of Bayer Schering's original allegation was anonymous market research data from 12 GPs in September 2007 and 3 hospital doctors in March 2007. In Bayer Schering's correspondence to the Panel, it had included a further survey of an additional 4 hospital physicians, conducted in December 2007, not previously provided to Lilly and of which it was unaware. This type of market research was a paper based questionnaire that was mass mailed by the agency. Doctors were asked to complete the survey, sign and return, upon which they were sent a gift token. There were a number of problems with this methodology. Firstly, the quality of the data was solely dependant on the accurate memory of the doctor and there was generally no additional supporting evidence or validation. Secondly, there was no guarantee that the form had been completed by a health professional. Thirdly, there was no targeting exercise to verify that physicians surveyed had actually been detailed in the last week. Finally, as the unique identifiers had been removed, it could not be concluded that these individuals were indeed unique. This was particularly important in this case where two identical comments, reported in March and December, were allegedly made by two separate specialist registrars in genitourinary medicine, which was a relatively small speciality. Lilly requested that the agency verified that these individuals were indeed not one and the same whilst maintaining confidentiality.

From the three surveys (total of 19 physicians), one respondent from general practice indicated that they recalled attending a meeting where 'New data on the reduction in CVD' was associated with tadalafil. There was no information to suggest that this was a Lilly promotional meeting or that Lilly was in anyway involved. A specialist registrar in genitourinary medicine, indicated that they recalled that 'small doses of Cialis protect vessels in high cardiovascular risk patients'. Again there was no additional detail to suggest that this message was delivered proactively by a Lilly representative. A second specialist registrar in genitourinary medicine, reported a similar message 'Low doses of Cialis protected cardiovascular system'. Therefore, in total, three physicians out of 19 surveyed made an association between Cialis and cardiovascular disease. However, this portion might represent a distorted and biased interpretation of the data, with little significance, as Lilly had no information as to the total number of agency market research waves conducted by Bayer Schering during 2007.

Lilly submitted that, although smaller dosage forms were licensed, only the standard doses of Cialis (10mg and 20mg) were available in the UK, so any allegation that Lilly promoted 'low doses' would not make commercial sense. There were a number of alternative reasons, all compliant with the Code as to why these three physicians would report an association between Cialis and cardiovascular disease. It had long been recognised that erectile dysfunction was often a consequence of general vascular disease or atherosclerosis, with patients therefore predisposed to conditions such as heart attacks, peripheral vascular disease and stroke. Atherosclerosis, or the laying down of plaque in the arterial wall, was thought to be linked to low grade inflammation of the vessel wall among other factors. The link between the enzyme PDE5 and dysfunction of the lining of the arteries (the endothelium) contributing to this inflammation was of huge scientific interest and increasing debate at congresses and meetings. In a literature search of 2007, there were 46 publications with 'tadalafil' and 'cardiovascular' identified as key words (Lilly's search was limited to English text and human subjects). Twenty articles in 2007, applying the same limitations, contained the keywords 'tadalafil' and 'endothelium'. Physicians therefore had wide access to such information on tadalafil and other PDE5 inhibitors, outside of any representative, through publications, independent scientific conferences and meetings, Lilly medical advisory boards, or in response to request for such data made to the Lilly medical/scientific services.

Whilst Lilly acknowledged that the comments of such physicians might be real, it remained confident that the source of this information was not a Lilly representative as suggested by Bayer Schering. Lilly submitted that the actions of its representatives were not in breach of Clauses 3.2 or 7.2. As previously stated, all of the tadalafil promotional material was on-licence.

In response to the alleged breach of Clause 9.1, Lilly agreed that inter-company dialogue took place as per correspondence (provided). It was noteworthy however that the case presented to the Panel differed from the original inter-company complaint (ie 3 months of market research vs 2 months). In addition, the nature of this complaint meant that robust evidence substantiating Bayer Schering's complaint was absent and hence any request for Lilly to provide company confidential documents such as sales material and briefing documents, was deemed disproportionate. Lilly hoped this reassured that all reasonable measures had been taken to address Bayer Schering's concerns and hence did not consider its previous actions to have breached Clause 9.1.

PANEL RULING

The Panel noted the parties' submission regarding agency monitoring reports and inter-company dialogue. The Panel noted that the monitoring reports

for March and September 2007 had been the subject of inter-company dialogue. A new report for December 2007 was also the subject of the current complaint and raised a closely similar matter. The Panel noted the Director's decision that inter-company dialogue had been unsuccessful.

The sole evidence provided by Bayer Schering comprised detail recall data from a small number of doctors. Three separate entries referred to Cialis and its cardiovascular effect. The Panel noted Lilly's submission about the survey's methodology and weight to be attached to such evidence.

The Panel accepted that it was difficult to know precisely what representatives were saying to health professionals. This was one reason why the Code required briefing material to be prepared.

None of the promotional or briefing materials provided referred to a possibility that Cialis protected vessels in high CV risk patients. Nor were doses other than 10mg and 20mg mentioned. The Panel was nonetheless concerned that physicians recalled that smaller doses of Cialis protected vessels but did not consider that this was consistent with the material provided by Lilly. There was no evidence that the entries referred to comments made by Lilly representatives.

The Panel noted that Bayer Schering had to establish its case on the balance of probabilities. Bayer Schering had referred to the '*possibility* that Cialis had been, and was being, promoted outside its licence in relation to cardiovascular conditions' (emphasis added). The Panel considered that Bayer Schering had not provided sufficient evidence to establish that Lilly was, on the balance of probabilities, promoting Cialis outside its licence as alleged. The Panel ruled no breach of Clauses 3.2 and 7.2. The Panel also ruled no breach of Clause 2.

With regard to the alleged breach of Clause 9.1 in relation to Lilly's refusal to supply information as requested or discuss conciliation, the Panel considered that there was no breach. There was no obligation for companies to discuss conciliation. There was only a requirement for the complainant to attempt inter-company dialogue prior to submitting a complaint to the Authority (Paragraph 5.2 of the Constitution and Procedure).

Complaint received 31 January 2008

Case completed 26 March 2008

CASE AUTH/2094/1/08

PRESCRIBING ADVISOR v SERVIER

Provision of samples and heart rate monitors

A prescribing advisor, on one of the Channel Islands, complained about the provision of samples of Procoralan and heart rate monitors by Servier.

The complainant stated that early last year Procoralan was turned down for inclusion on the island's prescribing list, which meant that it could not be prescribed at public expense. Servier representatives, however, offered a consultant cardiologist samples of Procoralan. A copy of the correspondence and paperwork was provided. The hospital's policy was that all samples must be received via pharmacy. Only medicines already on the formulary would be accepted. The pharmacy department was not asked by Servier's representative to handle these samples. The complainant alleged a breach of the Code because this attempt to supply samples did not comply with the hospital's requirements. It was an ill-disguised attempt to circumvent the approval process for new medicines. It was inconceivable that the Servier representative would not have known that Procoralan was turned down for use on the island.

The complainant further alleged that Servier had offered the consultant cardiologist heart rate monitors as an inducement to start patients on Procoralan.

The Panel noted Servier's submission that, to date, the samples had not been provided; there thus could be no breach of the Code and the Panel ruled accordingly.

With regard to the provision of heart rate monitors, the Panel noted that the representatives' briefing material stated '[The heart rate moniters] are not a promotional aid and therefore must be delivered in a separate call to a promotional call. You should not enter into a promotional discussion with the doctor when delivering the monitors'. The briefing notes were signed by 'The Procoralan Team' which the Panel considered could link the monitors to the promotion of Procoralan.

An email from the representative to the doctor provided by the complainant referred to the Procoralan samples and also stated 'I would like to thank you for your time…….. You should also be receiving your heart rate monitors by next week, let me know if they are useful to you'. The email concluded with a request for the name of another doctor so that the representative could '... keep him updated about Procoralan and Coversyl'. The Panel did not know what was said at the meeting. Nevertheless the email gave a poor impression. It referred to a promotional discussion and the provision of a medical good and implied that both had been discussed at the meeting. This was unacceptable as the provision of medical and educational goods and services must not be linked to the promotion of a medicine. The Panel considered that in the email the representative had not separated the provision of the heart rate monitors from the promotion of Procoralan. The representative had not maintained a high standard of conduct and thus a breach of the Code was ruled.

The Panel considered that heart rate monitors would enhance patient care and would be acceptable as long as their provision met the requirements of the Code. The Panel noted its comments about the email and the meeting. It also noted Servier's submission about the provision of the monitors and the instructions to representatives. There was no evidence that the monitors had been used as an inducement to prescribe. No breach of the Code was were ruled.

A prescribing advisor, on one of the Channel Islands, complained about the provision of samples of Procoralan (ivabradine) and heart rate monitors by Servier Laboratories Ltd. Procoralan was indicated for the symptomatic treatment of chronic stable angina pectoris in patients with normal sinus rhythm, who had a contraindication or intolerance to beta-blockers.

COMPLAINT

The complainant stated that early last year Procoralan was turned down for inclusion on the island's prescribing list, which meant that it could not be prescribed in either primary or secondary care at public expense. A GP and a consultant cardiologist had requested its approval. Neither appealed this decision, although they were permitted to do so.

In November 2007 Servier representatives met the consultant cardiologist and offered him samples of Procoralan to trial on some of his patients. A copy of the correspondence and paperwork was provided. However the island's hospital pharmacy was not asked to receive, store or dispense these samples. The hospital's policy on medicines was that all samples must be received via pharmacy. Only medicines already on the formulary would be accepted. The chief pharmacist and his deputy were never asked by Servier's representative to handle these samples.

The complainant alleged a breach of the Code because the Code stated that the offering of samples must comply with individual hospital requirements. This attempt to supply samples did not comply with the hospital's requirements and was in clear breach of the hospital's policy. It was an ill-disguised attempt to circumvent the approval process for new medicines. It was inconceivable that the Servier representative would not have known that Procoralan was turned down for use on the islands.

The complainant further alleged that Servier had offered the consultant cardiologist heart rate monitors as an inducement to start patients on Procoralan.

When writing to Servier the Authority asked it to respond in relation to Clauses 2, 9.1, 15.2, 17.8 and 18.1 of the Code.

RESPONSE

Servier submitted that, to date, the samples referred to by the complainant had not been provided to the consultant cardiologist. Correspondence between the representative and the cardiologist regarding the samples was via the doctor's personal/private email. In addition, the address provided by the cardiologist for receipt of the samples was the cardiologist's private clinic. Subsequently the cardiologist had independently, without Servier's knowledge, taken Procoralan to the hospital Drugs and Therapeutics Committee. The representative had not intended to supply the samples to the cardiologist for hospital use. In view of this Servier submitted that there was no breach of Clause 17.8 as the samples were not intended for the hospital; the representative knew that Procoralan had not been accepted on to the hospital's formulary. Therefore overall, Servier submitted that the representative had maintained high standards and was not in breach of Clause 15.2.

Servier submitted that it took pride in maintaining the highest standards at all times, and the representative faithfully adhered to this principle. There was thus no breach of Clause 9.1 of the Code.

Servier submitted that elevated heart rate had been associated with an increased risk of all-cause mortality and cardiovascular mortality in patients with pre-existing coronary artery disease and was recognised as an important factor in the management of angina pectoris (Graham *et al* 2007). Yet its value seen by cardiologists remained low. With respect to this Servier offered heart rate monitors as medical goods for patient use in the monitoring and management of heart rate in angina pectoris. The heart rate monitors were offered via a reply paid card, which was mailed to consultant cardiologists in the UK thus providing them all with the opportunity to request the item. The heart rate monitors were delivered by representatives in a non-promotional call as per the briefing notes; a procedure followed in this case. In addition, each heart rate monitor was provided with a 'Heart Rate Monitoring Form' for patient use, and an 'Angina Patient Heart Rate Follow-Up Form' for use by the doctor to allow appropriate heart rate recording and management of patients. The heart rate monitors were provided as an aid to patient care; there was no link between them and any Servier product. Servier had received spontaneous positive feedback about the provision of the monitors and their use in the management of patients with cardiac disease. Overall therefore, Servier submitted that there was no breach of Clause 18.1.

Servier stated that it was clear that none of this activity had brought discredit upon, or reduced confidence in, the pharmaceutical industry and thus there was no breach of Clause 2.

PANEL RULING

The Panel noted Servier's explanation about the arrangements between the representative and the doctor in relation to the samples. It did not know where the meeting had taken place. The delivery address was not the hospital. It might have been helpful if the sample request form was clear that the samples were to be provided for use with private patients and not NHS hospital use. Procoralan had a marketing authorization and could be promoted. It was not on the island's prescribing list which meant it could not be prescribed at public expense. It could however be prescribed for private patients. The Panel noted Servier's submission that, to date, the samples had not been provided to the requesting doctor for use in his private practice. Thus there could be no breach of Clause 17.8 and the Panel ruled accordingly.

With regard to the provision of heart rate monitors, the Panel noted that representatives' briefing material stated '[The heart rate moniters] are not a promotional aid and therefore must be delivered in a separate call to a promotional call. You should not enter into a promotional discussion with the doctor when delivering the monitors'. The briefing notes were signed by 'The Procoralan Team' which the Panel considered could link the monitors to the promotion of Procoralan.

The Panel examined the email from the representative to the doctor provided by the complainant. The email referred to the Procoralan samples to be used as a trial in patients over the forthcoming months. It also stated 'I would like to thank you for your time…….. You should also be receiving your heart rate monitors by next week, let me know if they are useful to you'. The email concluded with a request for the name of another doctor so that the representative could '... keep him updated about Procoralan and Coversyl'. The Panel did not know what was said at the meeting. Nevertheless the email gave a poor impression. It referred to a promotional discussion and the provision of a medical good and implied that both had been discussed at the meeting. This was unacceptable as the provision of medical and educational goods and services must not be linked to the promotion of a medicine. The Panel considered that in the email the representative had not separated the provision of the heart rate monitors from the promotion of Procoralan. The representative had not maintained a high standard of conduct and thus a breach of Clause 15.2 was ruled.

The Panel considered that heart rate monitors would enhance patient care and would be acceptable as long as their provision met the requirements of Clause 18 of the Code. The Panel noted its comments of about the email and the meeting. It also noted Servier's submission about the provision of the monitors and the instructions to representatives. There was no evidence that the monitors had been used as an inducement to prescribe. No breach of Clauses 18.1 and 18.4 was ruled.

The Panel did not consider that the circumstances amounted to a breach of either Clause 9.1 or Clause 2 and ruled accordingly.

Complaint received 31 January 2008

Case completed 5 March 2008

CASE AUTH/2096/1/08

ANONYMOUS v TRINITY-CHIESI

Fostair journal advertisement

An anonymous complainant alleged that a journal advertisement for Fostair (beclometasone and formoterol) issued by Trinity-Chiesi failed to display the non-proprietary name of the medicine immediately adjacent to the most prominent display of the brand name in the type size required by the Code.

The Panel noted the Code required that the non-proprietary name, or a list of the active ingredients using approved names where such existed appeared immediately adjacent to the most prominent display of the brand name in bold type of a size such that a lower case 'x' was no less than 2mm in height or in type of such a size that the non-proprietary name or list of active ingredients occupied a total area no less then that taken up by the brand name. The Panel noted that neither of these conditions had been met and thus ruled a breach of the Code.

An anonymous (and non contactable) complainant complained about an advertisement for Fostair (beclometasone and formoterol) (ref TRFOS20070526) issued by Trinity-Chiesi Pharmaceuticals Ltd published in Prescriber January 2008.

COMPLAINT

The complainant stated that he/she had recently been made aware of the details of the Code and in particular the need to have the non-proprietary name of the medicine immediately adjacent to the most prominent display of the brand name in bold type of a size such that a lower case 'x' was no less than 2mm high.

The complainant alleged that in the advertisement for Fostair this was not the case.

RESPONSE

Trinity-Chiesi confirmed that the lower case letters in the non-proprietary name, adjacent to the most prominent mention of the brand name, were less than 2mm high.

Trinity-Chiesi noted in the advertisement at issue, the associated text directly underneath the Fostair logo and non-proprietary name restated the non-proprietary name very prominently with lower case letters higher than 5mm. Trinity-Chiesi submitted that this clearly demonstrated that there was no deliberate attempt to make the non-proprietary name less prominent and mislead readers.

Trinity-Chiesi had subsequently taken immediate action to correct the advertisement to ensure that future editions of Prescriber and other journals carrying the same advertisement complied with the Code in this regard.

PANEL RULING

The Panel noted Clause 4.3 of the Code which required that the non-proprietary name, or a list of the active ingredients using approved names where such existed appeared immediately adjacent to the most prominent display of the brand name in bold type of a size such that a lower case 'x' was no less than 2mm in height or in type of such a size that the non-proprietary name or list of active ingredients occupies a total area no less then that taken up by the brand name. The Panel noted that neither of these conditions had been met. It thus ruled a breach of Clause 4.3 as acknowledged by Trinity-Chiesi.

Complaint received	11 February 2008
Case completed	11 March 2008

CASE AUTH/2098/2/08

VOLUNTARY ADMISSION BY ROCHE

Promotion of Herceptin and Avastin to the public

As a result of inter-company dialogue, Roche voluntarily admitted that it had promoted prescription only medicines to the public in that a one page article which it placed in the 2007 edition of In The Pink magazine referred to Herceptin (trastuzumab) and Avastin (bevacizumab). The article faced a one page corporate advertisement for Roche oncology.

In The Pink magazine was an annual consumer publication available in September/October to support Breast Cancer Awareness Month.

The Constitution and Procedure provided that the Director should treat a voluntary admission as a complaint if, inter alia, it related to a potentially serious breach of the Code. Advertising prescription only medicines to the public was regarded as a serious matter and the admission was accordingly treated as a complaint.

The Panel noted that in January 2007 Roche had been offered a chance to buy space for an advertisement and an article by the In The Pink editor. The Panel considered that at the outset these should have been seen by Roche as a single corporate package; instead the company viewed the two components as individual items which could be dealt with separately under the Code. In the Panel's view this initial failure to recognise that the article was paid-for space for which Roche would be responsible under the Code, together with the lack of formality and clear written agreements at the outset, led to the errors which occurred. An internal Roche email dated 30 January described the process. The advertisement was required by August and the article copy was required by July and '…we get to input and influence this (basically we can put an overview forward of key areas we'd like them to consider covering) and sign off on final copy'. An email from Roche to the publishers dated 31 January asked for confirmation of the exact process around the article. It did not appear that this point had been answered other than that the editor would be in touch soon regarding the article but in the meantime press releases could be forwarded to the editor. In August the magazine editor asked for press releases so as to decide what to cover in the article.

Roche sent the breast portfolio and relevant press releases on Avastin, Bondronat and Xeloda. This email stated that the article and advertisement were commissioned by Roche. In September Roche provided a number of press releases and backgrounders and asked to see the article before it went to print if this were possible. Roche submitted that it did not see the final article.

Of the two pages that were published in the In The Pink magazine, one simply stated 'Roche oncology working together to fight cancer'. This was the corporate advertisement submitted by Roche and had the company logo in the top right hand corner. The facing page was headed 'Pioneering an era of unprecedented benefit for women with breast cancer'. The Roche company logo appeared at the end of the heading. The article referred to Herceptin and Avastin as a new generation of medicines which transformed the outlook for women with breast cancer. It went on to discuss the positive effects of Herceptin and Avastin including on progression free survival which it described as unprecedented.

The Panel considered that the second page was an advertisement for Herceptin and Avastin, prescription only medicines. It was not an independent article; Roche had paid for the space and provided the information. Although the article had been written by a third party, Roche was nonetheless responsible for it. A breach of the Code was ruled. It thus followed that the advertisement also contained statements which would encourage members of the public to ask their health professionals to prescribe a specific prescription only medicine. A further breach was ruled.

The Panel considered that the generation of the advertisement demonstrated a lack of control and poor knowledge of the requirements of the Code. High standards had not been maintained. A breach was ruled. The Panel considered that companies should take particular care when producing material for the public. Roche had failed to exercise due diligence. On balance the Panel considered the conduct of company employees was such that they had brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

Roche Products Limited voluntarily admitted that a one page article which it placed in the 2007 edition of In The Pink magazine promoted Herceptin (trastuzumab) and Avastin (bevacizumab), both prescription only medicines, to the public. The article was next to a one page corporate advertisement for Roche oncology. Together the advertisement and the article formed a double page spread.

In The Pink magazine was an annual consumer publication with a potential circulation of about 75,000. The 2007 edition was available for six weeks over September and October to support Breast Cancer Awareness Month, and could be purchased in supermarkets and newsagents. Correspondence between Roche and the publisher outlining distribution and intended audience was provided.

COMPLAINT

Roche stated that as a result of a complaint from GlaxoSmithKline UK Limited about an advertisement and article in the 2007 edition of In The Pink it now voluntarily admitted of a breach of Clause 20 of the Code, with regard to promotion to the public.

Roche stated that regrettably, communication between it and the publishing company was not completely effective and as a result the article contained some promotional messages to the public. A copy of the article was provided.

Roche fully supported the Code and although unintentional and factually correct the article was clearly a breach of the Code and thus it decided to bring it to the Authority's attention.

The Constitution and Procedure provided that the Director should treat a voluntary admission as a complaint if it related to a potentially serious breach of the Code or if the company failed to take appropriate action to address the matter. Advertising prescription only medicines to the public was regarded as a serious matter and the admission was accordingly treated as a complaint.

When writing to Roche, the company was asked to respond in relation to Clauses 2, 9.1, 20.1 and 20.2.

RESPONSE

Roche did not contest breaches of Clauses 2, 9.1, 20.1 and 20.2.

Roche had undertaken a thorough investigation into the activities and communications leading up to the publication of the article. To allow a transparent view of these events Roche provided details of all events in chronological order and summarised them as follows:

Details of the article's production;

- The publishers approached Roche on 23 January 2007 regarding, a full page advertisement and article package.

- Roche agreed the funding on the understanding that the advertisement would be a corporate one and include no product branding. Roche requested approval of the article in correspondence with the publisher at this stage. However no formal agreement for Roche approval was written into the agreement.

  Roche noted that the corporate advertisement in the magazine complied with the Code and was certified in accordance with Clause 14.3. However, although the article was requested for approval when the project was set up, the lead individual was on sick leave when it was developed, so final approval was not sought.

- Payment for the package was sent in March 2007 upon receipt of an invoice from the publisher.

- No further action was taken until August.

- The lead individual on the article and main contact with the publisher was on unexpected sick leave when the publisher requested Roche's latest press releases relating to breast cancer upon which to base the article. At this point the project was managed by people who had no prior knowledge of the nature of the article and the fact that it was a paid-for article.

- Certified press releases (provided) for Roche oncology products licensed for use in breast cancer were sent to the publication upon request.

  The provision of the press releases occurred in two emails, offering a spectrum of information on all Roche breast cancer products. The second batch contained a 'targeted therapies' backgrounder which appeared to have formed the basis for the majority of the final article.

Roche submitted that the publisher then produced the article. Regrettably, due to a lack of continuity in the management of this project and no robust process to approve both advertisement and article together, the article was not requested for full copy approval and was incorrectly treated as responding to an independent article request, rather than a paid-for article.

Action already taken;

- When it realised the error Roche undertook an in-depth investigation to identify the events that might have led to this occurring.

- Roche also immediately contacted the publishing company to ensure that no unsold copies of the magazine were still in circulation (gaining written confirmation that all copies had been destroyed) and that no further copies could be made available to the public.

Compounding circumstances;

Roche submitted that its investigation showed no deliberate intent to breach the Code and promote to the public. Therefore, although Roche did not contest breaches of Clauses 2, 9.1, 20.1 and 20.2, it was important to explain the circumstances that led to the breach.

- Internal process training

  Roche submitted that the training at Roche when the project was undertaken did not sufficiently highlight the need for a formal contract to ensure full copy approval of paid-for articles. Therefore, although copy review was initially requested by Roche this was not chased or requested in a formal manner as it should have been.

- Inconsistent project management

  Unfortunately the Roche lead on this article was unexpectedly off sick in late August for two weeks

and in late September for around ten days. Therefore the press releases provided to the publisher were sent by people who did not know about the original agreement, or that the article had been paid for. However, an informal request to review the article was made again at this stage.

- Approval process

  Roche submitted that it currently had two separate processes for the approval of marketing led activities (such as advertisements) and PR activities. Had there been a system to approve the corporate advertisement and the article together as one item this error might have been averted. With the future compliance development plan this was being addressed as a priority.

- Agreement, payment, set up and delivery of package

  Roche submitted that the item was agreed with the publisher in January 2007 and paid for in March 2007 but nothing more happened until August 2007 when the advertisement and press releases were requested. This time delay, combined with the lead Roche contact being on sick leave, contributed to the series of events.

Roche fully understood that the above circumstances did not mitigate the breaches of the Code however it took this issue very seriously. A detailed overhaul of the company's standard operation procedures had been initiated to ensure that it had ongoing robust processes to ensure full compliance with the Code. These improvements would significantly reduce the risk of such incidents happening again in the future. Furthermore, as part of its ongoing partnership with the ABPI Roche was implementing a comprehensive compliance programme (provided).

PANEL RULING

The Panel noted that Roche had been offered an advertisement and an article by the In The Pink editor. An email from the publisher dated 23 January referred to the Roche brand fitting perfectly with the magazine which was described as a glossy annual magazine dedicated to Breast Cancer Awareness Month. The email made it clear that Roche was being offered the chance to buy space for an advertisement and an article. The Panel considered that at the outset the advertisement and article should have been seen by Roche as a single corporate package; instead the company viewed the two components as individual items which could be dealt with separately under the Code. In the Panel's view this initial failure to recognise that the article was paid-for space for which Roche would be responsible under the Code, together with the lack of formality and clear written agreements at the outset, led to the errors which occurred. In that regard the Panel did not accept that the passage of time and the change of personnel had contributed to the series of events. An internal Roche email dated 30 January described the process. The advertisement was required by August and the article copy was required by July and '…we get to input and influence this (basically we can put an overview forward of key areas we'd like them to consider covering) and sign off on final copy'. An email from Roche to the publishers dated 31 January asked for confirmation of the exact process around the article. It did not appear that this point had been answered other than that the editor would be in touch soon regarding the article but in the meantime press releases could be forwarded to the editor. In August the magazine editor asked for press releases for the article page so that the editor could decide what to cover in the article.

Roche decided to send the breast portfolio and relevant press releases on Avastin, Bondronat and Xeloda. This email stated that the article and advertisement were commissioned by Roche. In September Roche provided a number of press releases and backgrounders and asked to see the article before it went to print if this were possible. Roche submitted that it did not see the final article.

The Panel examined the two pages that were published in the In The Pink magazine. One simply stated 'Roche oncology working together to fight cancer'. This was the corporate advertisement submitted by Roche and had the company logo in the top right had corner. The facing page was headed 'Pioneering an era of unprecedented benefit for women with breast cancer'. The Roche company logo appeared at the end of the heading. The article referred to Herceptin and Avastin as a new generation of medicines which transformed the outlook for women with breast cancer. It went on to discuss the positive effects of Herceptin and Avastin including on progression free survival which it described as unprecedented.

The Panel considered that the second page was an advertisement for Herceptin and Avastin, prescription only medicines. It was not an independent article; Roche had paid for the space and provided the information. Although the article had been written by a third party, Roche was nonetheless responsible for it. A breach of Clause 20.1 was ruled. It thus followed, that the advertisement also contained statements which would encourage members of the public to ask their health professionals to prescribe a specific prescription only medicine. A breach of Clause 20.2 was ruled.

The Panel considered that the generation of the advertisement demonstrated a lack of control and poor knowledge of the requirements of the Code. High standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel considered that companies should take particular care when producing material for the public. Roche had failed to exercise due diligence. On balance the Panel considered the conduct of company employees was such that they had brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

Complaint received	**19 February 2008**
Case completed	**20 March 2008**

CASE AUTH/2105/3/08 *NO BREACH OF CODE*

ANONYMOUS DOCTOR v PROCTER & GAMBLE

Alleged promotion of Asacol to the public

An anonymous doctor complained that a poster, which had been placed in an outpatients department and designed to recruit patients into a clinical study, had caused numerous patients to ask for a once-daily prescription of Asacol (mesalazine). This had led to lengthy discussions with patients who did not fit into the trial criteria, but who still wanted the once-daily Asacol. As far as the complainant was aware Asacol which was marked by Procter & Gamble had not been licensed for once daily use. The complainant considered that recruiting patients in this way was extremely unethical; it not only gave false hope of a once-daily preparation, but caused unnecessary tension between patients and the clinician.

The Panel noted that Procter & Gamble's involvement with the trial was limited to the provision of an educational grant. The sponsor, an NHS trust, was responsible for the study. Procter & Gamble had played no role in the generation or placement of the poster at issue; it had been independently produced by the NHS trust that ran the study. The Panel thus decided that Procter & Gamble was not responsible for the poster and no breach of the Code was ruled.

An anonymous, non-contactable doctor complained about a poster which had appeared in the out-patients department of a hospital. The poster was headed 'CODA Trial – Colitis: Once daily Asacol'. Readers were told that remembering to take their tablets when their ulcerative colitis was in remission was hard and that taking tablets once daily would help although there was no evidence that this was as good as taking tablets two or three times daily. It was stated that the CODA trial was designed to investigate whether taking Asacol once daily was as effective as taking the same dose split three times during the day in preventing flares of disease in patients whose ulcerative colitis was in remission. The poster invited readers to participate in the study if their colitis was in remission but had flared in the past two years. The poster featured a cartoon picture of an elephant's head with a knot in its trunk.

Asacol (mesalazine) was marketed by Procter & Gamble Pharmaceuticals UK Limited. The summary of product characteristics (SPC) stated that in maintenance therapy three to six tablets were to be taken a day in divided doses.

COMPLAINT

The complainant stated that as far as (s)he was aware Asacol had not been licensed as a once-daily option. Although the poster stated that a once-daily preparation might not have any benefit, the picture used (an elephant never forgets!) and the highlighting of key words in the poster pointed towards better compliance.

The complainant submitted that the poster had caused numerous patients to ask for a once-daily prescription of Asacol. It had also caused the complainant unnecessary stress, as (s)he had had to have lengthy discussions with patients who did not fit into the trial criteria, but still insisted on having the once-daily preparation of Asacol. The very fact that the poster was placed in the patients' waiting area of the hospital meant that it was targeting the general public. This was a sure way of getting patients' attention.

The complainant stated that (s)he did not have an issue with pharmaceutical companies recruiting patients for their clinical trials, but it should be done appropriately. Physicians should be given the relevant information and then decide on the appropriate patients who should enter the trials. The complainant had not been briefed by Procter & Gamble on the CODA trial.

The complainant provided two photographs of the outpatient department showing the location of the poster in question. The complainant wanted to remain anonymous, as Procter & Gamble had funded many projects at his/her hospital and (s)he did not want to be identified as the whistle blower that led to the company withdrawing its support.

The complainant considered that this type of behaviour was extremely unethical; it not only gave patients the false hope of a once-daily preparation, but caused unnecessary tension between the patient and the clinician during clinics.

When writing to Procter & Gamble the Authority asked it to respond in relation to Clauses 2, 9.1, 20.1 and 20.2 of the Code.

RESPONSE

Procter & Gamble stated that it had neither sponsored the CODA trial nor played any role whatsoever in the production or placement of the poster.

Procter & Gamble explained that CODA (Colitis Once Daily Asacol) was a 12 month randomised, multicentre, parallel group single-blind study to assess the efficacy and safety of dosing mesalazine 800mg tablets at 2.4g once daily vs divided doses three times daily in the maintenance of remission of ulcerative colitis. The trial also included a compliance sub-study. The study protocol was approved by the Multi Centre

Research Ethics Committee (MREC) and the Medicines and Healthcare products Regulatory Agency (MHRA). Procter & Gamble had funded the study via an educational grant, which covered study medicine, regulatory consulting and financial support (employment of a central study co-ordinator, recruitment costs, etc).

The sponsor of the study was an NHS trust. The trust ran the study and was fully and independently responsible for the study protocol and the conduct and scientific evaluation of the study. The trust also owned all data and reports, including safety reporting and publishing of the results as obligated to do so under its national research governance framework for health and social care.

The poster was not Procter & Gamble's responsibility, nor was the company consulted on its content or its placement as referred to by the complainant. The poster was independently produced by the NHS trust. The wording was reviewed and approved by the Research Ethics Committee (REC); a copy of the approval letter forwarded to Procter & Gamble by the sponsor was provided.

The poster was distributed to the principal investigator at the hospital who completed contact details on the poster. These details were for the clinical nurse specialist at the hospital who was responsible for patient recruitment at the site (ie not a contact at Procter & Gamble). The poster was then placed by the clinical nurse specialist in the medical clinic which was where the gastroenterology clinic was held three days of the week. The position of the notice board had been specifically selected to be visible only to relevant patients with ulcerative colitis who might be interested in participating in the trial.

The complainant stated that the poster caused patients to ask for a currently not approved once daily prescription of Asacol. The purpose of the poster, however, was solely to raise awareness of the trial and aid recruitment. The poster clearly stated that the purpose of the trial was to investigate the open question, whether a once daily dosage regimen was equivalent to a divided dosage regimen; it also stated that there was currently no evidence that once daily was as good as divided dosing.

Procter & Gamble supported the complainant's statement that physicians should be given information to determine appropriate patients who should enter a trial; the company believed that the sponsor of the CODA trail did exactly this. Relevant staff at the hospital site and its research and development department were fully aware of the details of the CODA trial and had agreed to participate.

Procter & Gamble did not know why the complainant did not contact the clinical nurse specialist regarding the poster or the trial if it was causing unnecessary stress. It was also not clear how the complainant was able to discuss CODA trail inclusion and exclusion criteria with patients as these criteria were only known to the gastroenterology team and no other non gastroenterology physicians had contacted the clinical nurse specialist to request information.

In summary Procter & Gamble stated that it did not produce or distribute the poster and did not place it on the out-patient department's notice board.

The poster was produced independently by the NHS trust to aid patient recruitment. This was not a promotional activity. The wording in the poster was not promotional nor did it raise unfounded hopes of successful treatment.

With studies such as this, it was vital to maintain independence between the parties to give credibility to any results, to maintain high ethical standards and to ensure integrity should public scrutiny question the running of such a trial.

There was no promotion of a prescription only medicine and thus no breach of Clauses 20.1 or 20.2. Additionally, there had not been a failure to maintain high standards or any activity that would bring discredit upon, or reduce confidence in, the pharmaceutical industry and thus no breach of Clauses 9.1 or 2.

PANEL RULING

The Panel noted that it was a clearly established principle that companies were responsible under the Code for the activities of third parties acting on their behalf.

The Panel noted that Procter & Gamble's involvement in the CODA trial was limited to the provision of an educational grant and the sponsor, an NHS trust was responsible for the study. Procter & Gamble had played no role in the generation or placement of the poster at issue; it had been independently produced by the NHS trust that ran the study. The Panel thus decided that Procter & Gamble was not responsible for the poster and no breach of Clauses 20.1 and 20.2 was ruled. The Panel also ruled no breach of Clauses 9.1 and 2.

During its consideration of this case the Panel had some sympathy with the complainant's views; the poster did not refer to the NHS trust that had sponsored the study and the only product named was Procter & Gamble's Asacol. Although in this case Procter & Gamble had no involvement with the creation and placement of the poster, pharmaceutical companies similarly part funding studies would do well to remind those running studies that patient recruitment material must not inadvertently advertise prescription only medicines to the public or contain statements encouraging the public to ask a health professional to prescribe a specific prescription only medicine.

Complaint received 13 March 2008

Case completed 9 April 2008

CODE OF PRACTICE REVIEW – MAY 2008

Cases in which a breach of the Code was ruled are indexed in **bold type.**

2058/10/07	Primary Care Trust Chief Pharmacist v Pfizer	Champix journal advertisement	No breach	No appeal	Page 3
2060/10/07	**General Practitioner v Teva**	**Guidelines in Practice insert**	**Four Breaches Clause 7.2 Breaches Clauses 7.4 and 9.5**	**No appeal**	**Page 4**
2065/11/07 and 2066/11/07	**Anonymous representatives v Teva**	**Representative call rates**	**Breach Clause 15.9**	**No appeal**	**Page 14**
2071/11/07	**General Practitioner v Takeda**	**Competact and Actos leavepiece**	**Breach Clause 7.2**	**Appeal by respondent**	**Page 20**
2078/1/08	**Hospital Pharmacist v Pfizer**	**Promotion of Ecalta and Celsentri**	**Breach Clause 4.1**	**No appeal**	**Page 25**
2079/1/08 and 2080/1/08	Roche and GlaxoSmithKline v Sanofi-Aventis and Procter & Gamble	Actonel exhibition panel	No breach	No appeal	Page 27
2081/1/08	**Primary Care Trust Pharmacist v Teva**	**Guidelines in Practice supplement**	**Breach Clause 10.1**	**No appeal**	**Page 32**
2082/1/08	**Director/Medicines and Healthcare products Regulatory Agency/ Hospital Pharmacy Manager v Recordati**	**Tradorec XL 'Dear Dispensary Manager' letter**	**Breaches Clauses 9.1 and 9.5**	**No appeal**	**Page 36**
2083/1/08	**General Practitioner v Roche**	**Unsolicited email for Tamiflu**	**Breach Clause 9.9**	**No appeal**	**Page 38**
2084/1/08	Anonymous v Novartis	Arrangements for a meeting and conduct of representative	No breach	No appeal	Page 40
2085/1/08 and 2086/1/08	**Media/Director v Merck Sharp & Dohme and Schering Plough**	**Ezetrol insert in The Pharmaceutical Journal**	**Breaches Clause 7.2, 7.4 and 7.10**	**No appeal**	**Page 43**
2087/1/08	**UCB Pharma v Flynn Pharma**	**Medikinet XL 'Dear Doctor' letter**	**Breach Clause 7.2**	**No appeal**	**Page 47**
2088/1/08	**General Practitioner v AstraZeneca**	**Unsolicited email about Crestor**	**Breach Clause 9.9**	**No appeal**	**Page 51**

2092/1/08	**Bayer Schering Pharma v Lilly**	**Alleged promotion of unlicensed indication**	**No breach**	**No appeal**	**Page 53**
2094/1/08	**Prescribing advisor v Servier**	**Provision of samples and heart rate monitors**	**Breach Clause 15.2**	**No appeal**	**Page 56**
2096/2/08	**Anonymous v Trinity-Chiesi**	**Fostair journal advertisement**	**Breach Clause 4.3**	**No appeal**	**Page 58**
2098/2/08	**Voluntary admission by Roche**	**Promotion of Herceptin and Avastin to the public**	**Breaches Clauses 2, 9.1, 20.1 and 20.2**	**No appeal**	**Page 59**
2105/3/08	Anonymous Doctor v Procter & Gamble	Alleged promotion of Asacol to the public	No breach	No appeal	Page 62

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 Code covers the advertising of medicines to health professionals and administrative staff and also covers information about prescription only medicines made available to the 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 sponsorship of promotional meetings
- the sponsorship of scientific and other meetings, including payment of travelling and accommodation expenses
- 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
- the provision of information to the public either directly or indirectly, including by means of the Internet
- relationships with patient organisations.

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, or the provision of information to the public, 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.