PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

NUMBER 59 FEBRUARY 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.

Complaints in 2007 slightly down on 2006

In 2007 the PMCPA received 127 complaints as compared with 134 in 2006. There were 101 complaints in 2005, 119 complaints in 2004, 131 in 2003 and 127 in 2002.

The average number of complaints received each year since the PMCPA was established at the beginning of 1993 is 124, the numbers in individual years ranging from 92 in 1993 to 145 in both 1994 and 1997.

There were 122 cases to be considered in 2007, as compared with 128 in 2006. The number of cases usually differs from the number of complaints because some complaints involve more than one company and because some complaints do not become cases at all, usually because no *prima facie* case is established.

The number of complaints from health professionals in 2007 (57) exceeded the number from pharmaceutical companies (both members and non-members of the ABPI) (28). Complaints made by pharmaceutical companies are generally more complex than those from outside the industry, usually raising a number of issues.

Six complaints were made by members of the public, fifteen by pharmaceutical company employees and four by anonymous employees. There were two other anonymous complaints and two complaints were made by organisations.

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

'The ABPI Code: Still nifty at fifty?'

The Code celebrates its 50th anniversary this year and 'The ABPI Code: Still nifty at fifty?' campaign marking the anniversary will run throughout 2008. It will target the pharmaceutical industry, MPs, health professionals, patient organisations and PR and marketing professionals.

The ABPI Code first came into operation on 2 October 1958 and has been amended many times over the years. The first edition of the Code (called the Code of Sales Promotion Practice for Medical Specialities in the United Kingdom) has expanded from being only two pages long to the 33 pages of the current Code. Transparency has also increased over the years with more and more detail being published in case reports – since 1995 case reports have included more or less all that was stated by the parties involved.

The 'Nifty at fifty?' campaign will look back over the past 50 years, examining how the Code and regulatory environment has changed, as well as looking at the future of self regulation of prescription medicines in the UK. The central focus point of the campaign will be Code Awareness Week which is planned to take place in early October 2008. This will be an expanded version of Code Awareness Day which has run successfully for the past two years. During the week employees from pharmaceutical companies across the UK will once again unite to talk to health professionals and other stakeholders about the Code. An event in central London marking 50 years since the Code first came into operation is also planned.

Nigel Brooksby, President of the ABPI said: 'The forthcoming 50th anniversary

Continued overleaf

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Code awareness campaign wins PMEA award

The Code awareness campaign, 'It Takes Two to Tango', won the Judges' Special Recognition Award at the Pharmaceutical Marketing Effectiveness Awards (PMEA) and was highly commended in the Innovation Award category.

The 'It Takes Two to Tango' campaign, run by Santé Communications in 2006 on behalf of the ABPI and the PMCPA, aimed to raise awareness of the Code amongst doctors and others. The first ever Code Awareness Day took place on 25 April 2006 as part of this campaign. On this day more than 8,000 sales representatives from 50 pharmaceutical companies across the UK talked to health professionals about the Code.

Highlights from the day included:

- 7,500 clinicians were exposed directly to Code Day messages at two major congresses.
- Over 22,000 doctors were sent personal e-alerts.
- A targeted media campaign resulted in more than 15 features.
- A Parliamentary Motion supporting Code Awareness Day and the Code was signed by 41 MPs.
- Many companies ran in-house events for staff.

The PMEA judges said that this was a truly great campaign that handled a profoundly challenging topic comprehensively, with creativity and great thought. Using stakeholder management to make this campaign happen was praised as phenomenal.

'It Takes Two to Tango' also won the Communiqué award for Best Professional Campaign earlier this year and the campaign to raise awareness of the Code is ongoing. The second Code Awareness Day took place on 15 May 2007. Nurses and pharmacists are now also being targeted alongside doctors as part of this campaign.

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, 28 April 2008
Monday, 2 June 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:

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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.

'The ABPI Code: Still nifty at fifty?'continued

of the Code and the success of self regulation shows that the pharmaceutical industry is fully committed to high ethical standards in its promotion of prescription medicines. Transparency and accountability have increased considerably over the past 50 years. The requirements of the Code have also been tightened up, especially in recent years, which is further proof of the industry's commitment to operating professionally and ethically. This anniversary provides a great opportunity to look at how far we've come as an industry and to examine where we go from here.'

A revised version of the ABPI Code will come into operation on 1 July 2008.

Act now if you want to continue to receive the printed Code of Practice Review

In the November Review it was noted that as the Review is available on the relaunched PMCPA website (www.pmcpa.org.uk) recipients might no longer wish to be sent the printed version. The printed May Review will only be sent to those that have contacted the PMCPA, so if you would like to continue to receive the printed version, please tell the PMCPA so, preferably by email (lmatthews@pmcpa.org.uk) or by telephone (020 7747 8885) stating the number of copies you would like.

Printed copies will continue to be sent to pharmaceutical company chief executives.

Improved access to advice and training on the ABPI Code

You can now have instant access to the latest advice on the Code following the introduction of a new electronic alert system on the recently relaunched PMCPA website. The 'Latest advice on the Code' section of the website is also searchable by topic. In addition, training seminars on the Code can now be booked through the new online booking system which you can access from the 'Training on the Code' page of the website.

Anyone can sign-up to receive free PMCPA e-alerts at www.pmcpa.org.uk. Subscribers can choose to be alerted when advice on the Code, information about ongoing or completed cases, Code of Practice Reviews, public reprimands and corrective statements and news and events are added to the website. Subscribers manage their own preferences online.

CASE AUTH/2007/5/07

TRINITY-CHIESI v TEVA

Qvar leavepiece

Trinity-Chiesi alleged that the claim 'Twice as many symptom-free days' [compared with CFC beclometasone (BDP)] in a leavepiece for Qvar issued by Teva was not a fair and balanced representation of the available published evidence. Qvar was a CFC-free BDP inhaler for asthma. The claim was referenced to Price *et al* (2002). Price *et al* cited Fireman *et al* (2001) as principally responsible for reporting on the clinical and safety aspects of the open label study in question and therefore statements from Fireman *et al* regarding efficacy or safety were considered by Trinity-Chiesi to be important in relation to this study.

Trinity Chiesi alleged that in highlighting Fireman *et al*, Teva had largely ignored three key randomised, double-blind, double dummy studies. For example, Gross *et al* (1999) reported no difference between Qvar and equipotent doses of CFC-BDP when symptom-free days were assessed during the three month study involving 347 asthma patients. Additionally, no difference in the incidence of asthma symptoms was observed between asthma patients treated with Qvar compared with those treated with equipotent does of CFC-BDP in another two similarly designed studies (Magnussen *et al* 2000 and Davies *et al* 1998).

Furthermore, Fireman *et al* reported no significant differences in changes from baseline in the percentage of days without wheeze, shortness of breath or chest tightness throughout the study, whereas there was a statistically significant difference in the percentage of days without cough in favour of Qvar. Importantly, Fireman *et al* stated that although the result was statistically significant, it was probably not clinically significant. Teva had not acknowledged this important point in its material. This unquestionably cast doubt on the clinical significance of the claim.

Finally, assessment of symptom-free days was not stated to be a primary endpoint in Fireman *et al* therefore Trinity Chiesi alleged that only highlighting this data was misleading especially as no differences between Qvar and equipotent doses of CFC-BDP were observed in terms of efficacy and tolerability.

The Panel noted that the claim in question was referenced to Price *et al* which was a pharmacoeconomic study based on the results of Fireman *et al*.

Fireman *et al* examined whether asthmatic patients with symptoms controlled with CFC-BDP could be switched to CFC-free BDP at half the CFC-BDP dose without *inter alia*, adversely affecting the control of asthma symptoms. The authors demonstrated an overall increase in the percentage of symptom-free days (without wheeze, shortness of breath or chest tightness) between baseline and month 12 in the CFC-free BDP group (11.5%) and the CFC-BDP group (4.6%). No significant differences in the change from baseline in percentage of symptom free days were seen throughout the study. There were slight differences between CFC-free BDP and CFC-BDP in percentage of days without cough which although statistically significant at weeks 1 to 2 and at months 7 to 8 were described as probably not clinically significant. During months 7 to 8 patients on CFC-free BDP had a significantly greater proportion of nights without sleep disturbance than patients on CFC-BDP. The study concluded that asthma control was maintained in patients switched from CFC-BDP to CFC-free BDP.

Price *et al* re-examined Fireman *et al* for the cost effectiveness study. Price defined 'symptom-free day' as the absence of all of the following: wheeze, cough, shortness of breath, and chest tightness in one day including overnight. Patients in the CFC-free BDP group had a higher median percentage of symptom-free days than patients in the CFC-BDP group (42.4% v 20%; p=0.006). This equated to three symptom-free days per week in the CFC-free BDP group compared with 1.4 in the CFC-BDP group. The mean data which showed that the percentage of symptom-free days at 12 months was 45.6% (CFC-free BDP) and 35% (CFC-BDP), showed no statistically significant difference between the two treatment groups. This mean data appeared to be that which Fireman *et al* had used to report an increase from baseline of 11.5% (CFC-free BDP) and 4.6% (CFC-BDP) in percentage of days without wheeze, shortness of breath and chest tightness.

The Panel noted that, on a re-examination of the clinical data by Fireman *et al*, Price *et al* had reported statistically significantly more symptom-free days for patients taking CFC-free BDP compared with those taking CFC-BDP. The study authors had used a median percentage. The mean percentage did not show a statistically significant difference. The primary clinical data had not reported such a difference although there was a trend in favour of CFC-free BDP. Other studies (Davies *et al*, Gross *et al* and Magnussen *et al*) although shorter in duration (12 weeks or less) had demonstrated equivalent control of asthma for CFC-free BDP and CFC-BDP. Price *et al* was the only study to report that CFC-free BDP produced 'twice as many symptom-free days' as CFC-BDP. Overall

the Panel did not consider that the data was sufficiently robust to support such a strong claim and in that regard the claim 'Twice as many symptom-free days' was misleading in breach of the Code.

Upon appeal by Teva, the Appeal Board noted that Fireman *et al* evaluated whether asthma patients with symptoms controlled with CFC-BDP could be switched to CFC-free BDP at half the CFC-BDP dose without, *inter alia*, adversely affecting the control of asthma symptoms. The authors recorded that there were no consistent differences between the treatment groups with regard to individual asthma symptoms (wheeze, cough, shortness of breath and chest tightness) or daily use of reliever inhalers. Both groups recorded an increase in percentage of symptom-free days between baseline and one year (CFC-BDP 4.6% vs CFC-free BDP 11.5%). The authors concluded that asthma control was maintained in both groups.

Based on the clinical data generated by Fireman *et al*, Price *et al* compared the cost effectiveness of CFC-free BDP with CFC-BDP. Price *et al* assessed asthma symptoms in terms of symptom-free days which was a composite end point defined as the absence of all of the following: wheeze, cough, shortness of breath and chest tightness, in one day (including overnight). A table of data recorded the percentage symptom-free days and showed at baseline the median percentage symptom-free days in the CFC-free BDP group was 21.4% [95% confidence interval 14.3-28.6] and in the CFC-BDP group it was 12.7% [6.7-28.6] (p=0.226), ie there was almost a two fold difference between the groups at baseline. This difference was maintained throughout the study such that after one year the median percentage symptom-free days in the CFC-free BDP group was 42.4% [32.1 – 57.9] and 20% [3.8 – 37.9] in the CFC-BDP group. The Appeal Board noted that the confidence intervals overlapped. It was this data which formed the basis of the claim 'Twice as many symptom free days'.

The Appeal Board did not consider that Price *et al* was sufficiently robust as to support the claim 'Twice as many symptom free days'. The data had been derived from a pharmacoeconomic evaluation of primary clinical data in which no difference between CFC-free BDP and CFC-BDP in terms of asthma control had been shown. There was no indication that Price *et al* had been powered to detect a statistical difference in percentage symptom-free days; there had, in any case, been a two-fold difference between the two treatment groups at baseline in this regard, a difference which was present at the end of the study. The Appeal Board considered that given the data on which it was based the claim at issue was misleading and upheld the Panel's ruling of a breach of the Code.

Trinity-Chiesi Pharmaceuticals Ltd complained about the promotion of Qvar by Teva UK Limited. Qvar was a CFC-free beclometasone diproprionate (BDP) inhaler for asthma. A number of allegations were made about a number of materials. Each was carefully examined and following protracted correspondence with both parties the Director decided that the only matter upon which the requirements for inter-company discussion in Paragraph 5.2 of the Constitution and Procedure had been met related to a claim 'Twice as many symptom-free days'.

The material at issue was a leavepiece (ref IV/QV/CNL/12/06A and IV/QV/CFC/01/07) stated by Trinity-Chiesi to be recently delivered by a Teva representative to a health professional. Trinity-Chiesi supplied Clenil Modulite and Pulvinal Beclometasone.

COMPLAINT

The claim 'Twice as many symptom-free days' was referenced to Price *et al* (2002). Price *et al* cited Fireman *et al* (2001) as principally responsible for reporting on the clinical and safety aspects of the open label study in question and therefore statements from Fireman *et al* regarding efficacy or safety were considered by Trinity-Chiesi to be important in relation to this single study.

Trinity-Chiesi alleged that the claim 'Twice as many symptom-free days' was not a fair and balanced representation of the available published evidence. Teva had highlighted data from a 12 month randomised, open label trial (Fireman *et al*) and largely ignored the results from three key randomised, double-blind, double dummy studies. For example, Gross *et al* (1999) reported no difference between Qvar and equipotent doses of CFC-BDP when symptom-free days were assessed during the three month study involving 347 asthma patients. Additionally, no difference in the incidence of asthma symptoms was observed between asthma patients treated with Qvar compared with those treated with equipotent does of CFC-BDP in another two similarly designed studies (Magnusson *et al* 2000 and Davies *et al* 1998).

Furthermore, Fireman *et al* reported that no significant differences were observed in changes from baseline in the percentage of days without wheeze, shortness of breath or chest tightness (ie three of the four symptoms) throughout the study, whereas there was a statistically significant difference in the percentage of days without cough in favour of Qvar. Importantly, Fireman *et al* stated that although the result was statistically significant, it was probably not clinically significant. Teva had failed to acknowledge this important point in its material. This unquestionably cast doubt on the clinical significance of the claim.

Finally, assessment of symptom-free days was not stated to be a primary endpoint in Fireman *et al* therefore only highlighting this data in Qvar promotional material was alleged to be misleading especially as no differences between Qvar and equipotent doses of CFC-BDP were observed in terms of lung function parameters (usually primary efficacy endpoints) and tolerability.

In summary, Teva had not discussed any of the other relevant published data mentioned above and had selected data that did not reflect all the available evidence. This was misleading and not balanced, in breach of Clause 7.2 of the Code.

RESPONSE

Teva stated that Trinity-Chiesi was incorrect in its description of Gross *et al* on several accounts:

1 Gross *et al* was not a double-blind double-dummy study which was clearly stated in the 'Methods' and 'Discussion' sections.

2 Patients in Gross *et al* were a different patient population. Patients had uncontrolled asthma symptoms, whilst in the Fireman/Price study the patients' asthma symptoms were stable for one month prior to entry into the study and were simply randomised to receive the study therapies.

3 The number of patients in Gross *et al* that received CFC-free BDP was only 113 patients compared to 354 in the Fireman/Price study. The sample size was so small in Gross *et al* that a difference in symptom-free days would not be expected.

4 Gross *et al* was a very short-term study of only 12 weeks and to demonstrate an increase in symptom-free days between therapies a longer study period was required. This was why a 12-month study was conducted several years later and a positive result was demonstrated owing to the appropriate study period of 12 months' duration.

The other two papers quoted by Trinity-Chiesi, Magnussen *et al* and Davies *et al* also were of small sample size, short duration (12 weeks), were in widely differing patient groups and used variable doses. These used different criteria for patients enrolled, and different study conditions to those reported in Fireman/Price. The differences compared to Fireman/Price were;

1 Davies *et al* enrolled patients with moderately severe uncontrolled asthma symptoms and delivered doses of 800mcg day CFC-free BDP and 1500mcg/day CFC-BDP over a 12-week study period.

2 Gross *et al* enrolled patients with uncontrolled asthma symptoms and delivered doses of 400mcg/day CFC-free BDP and 800mcg/day of CFC-BDP over a 12-week study period.

3 Magnussen *et al* although enrolled patients with stable moderate asthma did not use equipotent doses as stated by Trinity-Chiesi but used higher CFC-doses which would militate against demonstrating a benefit in favour of CFC-free BDP. The study delivered doses of 400mcg/day CFC-free BDP and 1000mcg/day of CFC-BDP for a 10-week period.

Teva submitted that it was quite clear that none of the three studies quoted were directly comparable to the data from Fireman/Price and were therefore irrelevant to the interpretation of Fireman/Price. This point had been made several times to Trinity-Chiesi but had been ignored.

In addition Teva believed that the comments relating to its ability to support the claim with Price *et al* were erroneous as Trinity-Chiesi had ignored the central hypothesis as declared by the authors. It was rather difficult to understand that Trinity-Chiesi would not accept conclusions from a study published by leading experts in the field that had been vetted and agreed by the journal referees and had been deemed to be correct and worthy of publication by a prestigious journal that was well respected and widely read.

1 The hypothesis tested was directly linked to the study design and methodology employed, this in turn was directly linked to the results and any subsequent promotional claims for a product had been referenced to appropriate clinical studies.

2 In Price *et al* the concept of symptom-free days was based on improving the patients' ability to lead a normal life. The National Asthma Education and Prevention Program in the USA recommended the measure 'symptom-free day' as the principle outcome measure for cost-effectiveness analysis of asthma interventions. This was recognised in the forthcoming National Institute for Health and Clinical Excellence (NICE) review on inhaled corticosteroids (ICS) and long acting beta agonists (LABA) for the treatment of chronic asthma in adults and children 12 years and over: systematic review and economic analysis. The General Practice Airways Group also noted that 'Much of the analysis is based on studies with endpoints that have little meaning in the day to day asthma clinic; this is a particular problem where an economic analysis is attempted. Randomised clinical trials have traditionally been carried out on patients who have to fulfil very strict criteria drawn from secondary care and who do not represent the bulk of asthma patients seen in primary care.'

Teva disputed Trinity Trinity-Chiesi submission that Fireman *et al* was important in relation to safety and efficacy, as the hypothesis of the study was the 'Evaluation of the long term (12 months) efficacy and safety of switching patients with asthma maintained on a stable dose of CFC-BDP pMDI to therapy with [CFC-free BDP] at approximately half their previous daily dose of CFC-BDP'. Teva however disputed that this study should be used in relation to a promotional claim based on symptom-free days, as it clearly did not investigate symptom-free days as a primary end point nor did it provide statistical analysis of symptom-free days. All claims relating to symptom-free days were referenced to the more detailed analysis (pharmacoenconomics) conducted by Price *et al*.

Teva summarized Price *et al* as follows: The objective was to compare the cost effectiveness of CFC-free BDP in patients with chronic stable asthma previously receiving CFC-BDP, from the perspective of a healthcare provider.

Symptom-free days were one of the internationally recognised outcome measures on which the economic assessments were made. Price *et al* clearly stated in the introduction to the study the rationale and support for the approach taken.

The data were analysed directly from the audited dataset of this trial. The data were not normally distributed and therefore a non-parametric statistical test was used. This was the correct method to use to analyse data of non-gaussian distribution.

As with all non-parametric statistical tests median results were presented. These were a different measure than used in Fireman *et al* study. The median values of the number of symptoms-free days were 42.4 days for patients receiving Qvar and 20 days for patients receiving CFC-BDP; p=0.006 at 12 months.

Teva stated that the objective of Fireman *et al* was to evaluate the long term (12 months) efficacy and safety of switching patients with asthma maintained on a stable dose of CFC-BDP pMDI to therapy with CFC-free BDP at approximately half their previous dose of CFC-BDP.

The efficacy measures were; patient diary card of morning and evening peak expiratory flow rate, daily asthma symptoms, sleep disturbance, number of times a ß2-agonist was used and spirometry for pulmonary function. The safety measures were; laboratory tests, including serum osteocalcin, morning plasma cortisol levels. Of the 473 patients randomised at entry into the study 354 received Qvar (CFC-free BDP) and 119 received CFC-BDP. The paper reported a statistical analysis of the individual listed symptoms of wheeze, shortness of breath or chest tightness and this was expressed as the percentage of symptom-free days (rather than individual symptom-free days). The percentage of symptom-free days experienced by patients in each treatment group were not significantly different. There was a significant difference in favour of CFC-free BDP in the percentage of days without cough and nights without sleep disturbance during months 7 to 8. The authors stated that although these differences demonstrated statistical significance they were probably not clinically significant. Symptom-free days were discussed by describing the mean percentage of symptom-free days experienced by patients in both treatment groups; 11.5% in the CFC-free BDP group and 4.6% in the CFC-BDP group. No further statistical analysis was performed, the more detailed analysis was reported by Price *et al*. Fireman concluded that the increase in 'symptom-free days' in the patients who received CFC-free BDP compared with those that received CFC-BDP was greater than a 'two fold increase'.

Teva firmly believed that Price *et al* substantiated the claim twice as many symptom-free days. Fireman *et al* and other studies did not need to be discussed as they did not have symptom-free days as a primary endpoint. Thus there was no breach of Clause 7.2.

The measurement of 'symptom-free days' in Price *et al* was a totally different measure from the prevalence of individual symptoms in patients as reported in Fireman *et al*.

Price *et al* interrogated the dataset to investigate the pharmacoeconomic aspects. Fireman *et al* interrogated the dataset to investigate safety and efficacy as measured by various primary endpoint measures detailed in the methods section of the study design. Teva therefore concluded that symptom-free days, a composite measure was a totally different measure from the prevalence of individual symptoms in patients, the two outcomes were unrelated and had no bearing on each other. It did not accept that the use of symptom-free days was either inappropriate or misleading.

Teva concluded by stating that the three studies quoted by Trinity-Chiesi to support its position had:

- Hypotheses that looked at efficacy and were powered to look at equivalence between CFC-free BDP and CFC-BDP. The studies did not have primary or secondary endpoints looking at symptom-free days.
- Had differing patient populations, namely uncontrolled asthma patients.
- Were of short duration 10-12 weeks.
- Magnussen *et al* and Davies *et al* did not record data on symptom-free days. In Gross *et al* the number of symptom-free days was recorded, this was not a primary endpoint in the study analysis or of a pharmacoeconomic investigation. The patient populations were also evaluated in different ways.

The claim was referenced to Price *et al* which was appropriate as the hypothesis of the study investigated was pharmacoeconomic and related to symptom-free days.

Despite extensive literature searches Teva had not found any other study that presented symptom-free data in patients with well controlled asthma over a 12-month period that received Qvar and CFC-BDP.

Teva therefore did not believe it was misleading to use Price *et al* as the reference and it was fair and balanced as it accurately reflected the available data on symptom-free days. Teva denied a breach of Clause 7.2.

PANEL RULING

The Panel noted that the claim in question appeared, beneath the heading 'Doing more for your patients' on the leavepiece IV/QV/CFC/01/07. The claim was referenced to Price *et al* which was a pharmacoeconomic study based on the results of Fireman *et al*.

The Panel noted that Fireman *et al* examined whether asthmatic patients with symptoms controlled with CFC-BDP could be switched to CFC-free BDP at half the CFC-BDP dose without *inter alia*, adversely affecting the control of asthma symptoms. The authors demonstrated an overall increase in the percentage of symptom-free days (without wheeze, shortness of breath or chest tightness) between baseline and month 12 in the CFC-free BDP group (11.5%) and the CFC-BDP group (4.6%). No significant differences in the change from baseline in percentage of symptom free days were seen throughout the study. There were slight differences between CFC-free BDP and CFC-BDP in percentage of days without cough which although

statistically significant at weeks 1 to 2 and at months 7 to 8 were described as probably not clinically significant. During months 7 to 8 patients on CFC-free BDP had a significantly greater proportion of nights without sleep disturbance than patients on CFC-BDP. The study concluded that asthma control was maintained in patients switched from CFC-BDP to CFC-free BDP.

Price *et al* re-examined Fireman *et al* for the cost effectiveness study. Price defined 'symptom-free day' as the absence of all of the following: wheeze, cough, shortness of breath, and chest tightness in one day including overnight. As percentage symptom-free days were not normally distributed, median percentage symptom-free days were compared. By the end of the study patients in the CFC-free BDP group had a higher median percentage of symptom-free days than patients in the CFC-BDP group (42.4% v 20%; p=0.006). This equated to three symptom-free days per week in the CFC-free BDP group compared with 1.4 in the CFC-BDP group. The mean data which showed that the percentage of symptom-free days at 12 months was 45.6% (CFC-free BDP) and 35% (CFC-BDP), showed no statistically significant difference between the two treatment groups. This mean data appeared to be that which Fireman *et al* had used to report an increase from baseline of 11.5% (CFC-free BDP) and 4.6% (CFC-BDP) in percentage of days without wheeze, shortness of breath and chest tightness.

The Panel noted that, on a re-examination of the clinical data by Fireman *et al*, Price *et al* had reported statistically significantly more symptom-free days for patients taking CFC-free BDP compared with those taking CFC-BDP. The study authors had used a median percentage. The mean percentage did not show a statistically significant difference. The primary clinical data had not reported such a difference although there was a trend in favour of CFC-free BDP. Other studies (Davies *et al*, Gross *et al* and Magnussen *et al*) although shorter in duration (12 weeks or less) had demonstrated equivalent control of asthma for CFC-free BDP and CFC-BDP. Price *et al* was the only study to report that CFC-free BDP produced 'twice as many symptom-free days' as CFC-BDP. Overall the Panel did not consider that the data was sufficiently robust to support such a strong claim and in that regard the Panel considered that the claim 'Twice as many symptom-free days' was misleading. A breach of Clause 7.2 was ruled.

APPEAL BY TEVA

Teva submitted that this whole process became very drawn out, and one feature had been the way in which Trinity-Chiesi had written a very large number of letters in which it continually changed the basis of its complaint. Teva had provided robust answers to all of them. Additionally, some of the comments in the ruling appeared to be inconsistent or either incorrect and/or misleading.

Teva submitted that there appeared to be little acceptance or acknowledgement that the recording of individual symptoms, which included wheeze, cough, shortness of breath and chest tightness, were not interchangeable with the recording of symptom-free days and that they measured different outcomes.

Teva submitted that the studies listed by Trinity-Chiesi were not comparable and did not provide any relevant data relating to the incidence of symptom-free days in the different treatment groups. In addition, the ruling in its current form would have major implications on the way research-based companies could interpret data. This would put such companies at a disadvantage to companies that conducted minimal research and then tried to invalidate extensive studies of competitor companies and which, as in this case, demonstrated benefit to patients in a pragmatic real-life setting.

The claim 'Twice as many symptom-free days' had been used on large numbers of materials in the promotion of Qvar since 2004 and no health professional or company other than Trinity-Chiesi had complained about it.

Inconsistencies in the Panel's ruling

Gross was 'double-blind' in design

Teva submitted that the Panel's ruling provided a detailed analysis of several studies that Trinity-Chiesi claimed to demonstrate different outcomes but they were incorrectly categorised in the initial complaint. Despite several letters from Teva, Trinity-Chiesi had continued to misrepresent the studies.

The complainant alleged that 'Teva had highlighted data from a 12 month randomised, open-label trial (Firemen *et al*) and largely ignored the results from three key randomised, double-blind, double-dummy studies' (ie Gross 1999, Davies 1998 and Magnussen 2000). This statement was false as Gross *et al* was not a double-blind, double-dummy study. Gross *et al* clearly 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'. The authors seemed to claim that the study was blinded in some way but provided no details as to how this was achieved. In the 1990s there was a vogue to call a study 'single-blinded' if the patient was not told which 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 used to deliver CFC-free-BDP and CFC-BDP had different attributes as the products were present in solution and suspension respectively and had different shapes of canisters. Therefore, Teva submitted that in the absence of any details extreme caution must be exercised in relation to the claim that Gross *et al* was a blinded study as by today's standards it would be probably classed as an open-label study, as was Fireman *et al*/Price *et al*.

Teva submitted that the complaint was incorrect and misleading which unfortunately seemed to be a relatively common occurrence in the letters from

Trinity-Chiesi. Teva questioned why any company would misrepresent studies in this way but it appeared that by doing so it was seeking to strengthen its complaint in an inappropriate manner. Teva regarded this as unacceptable practice.

Parametric statistical methods

Teva submitted that the Panel's ruling stated in reference to Price *et al* that 'The mean data which showed that a percentage of symptom-free days at 12 months was 45.6% (CFC-Free BDP) and 35% (CFC-BDP), showed no statistically significant treatment differences between the two treatment groups'. This statement was untrue and was derived from an invalid use of statistical methodology.

- There was no statistical analysis conducted to determine whether the difference in mean values was statistically significant and this was clearly stated by Fireman *et al* and Price *et al*. Fireman *et al* stated that differences between treatment groups were examined statistically only for individual symptoms recorded on the case record forms. The results for symptom-free days were presented without any analysis and without comment on whether they were significant or not.

- The symptom-free days data was clearly stated by Price *et al* to have a non-Gaussian distribution and therefore it was inappropriate to consider the mean and standard deviation as an appropriate measure of the data distributions in the two treatment groups. This was clearly stated in Price *et al* and because mean and median were so far apart, non-parametric tests were required.

- If a t-test would have been performed on the data, it would have been highly significant as a t-test was more powerful than the Mann Whitney U-Test. However it would have been inappropriate to do so as the data distribution was not appropriate for use of the specific test.

- Neither Price *et al* nor Fireman *et al* conducted any statistical analysis on symptom-free days using the mean values and this was clearly indicated in the text and tables of both manuscripts.

Teva submitted that this error could be traced back to the way in which Trinity-Chiesi had conducted these complaints and it was inconceivable that a pharmaceutical company would be unaware of these basic facts. As previously pointed out to Trinity-Chiesi on several occasions Teva assumed that it was attempting to mislead the Panel.

'The mean percentage did not show a statistically significant difference'

Teva submitted that this statement in the last paragraph of the Panel's ruling was also untrue as no statistical analysis was performed in the way described in the ruling.

Review of statistical methodologies required for the analysis and interpretation of data that did not have normal (Gaussian) distribution

Teva submitted that even before a clinical trial was started power size was calculated using earlier studies which provided evidence of the variance of the data that would be studied. When a clinical trial was completed, the results were analysed using well defined statistical methodologies, supported by detailed quality assurance and internal audit. This process was required by all regulatory authorities and ensured that the results were robust and could be used to support the product that was the subject of the study. In this process one of the most important decisions that had to be taken was the choice of clinical statistical methodologies that were employed in the analysis.

Statistical test selection and data distribution

Teva submitted that to select an appropriate statistical test it was imperative to be aware of the distribution of the values presented in the data-sets because tests made assumptions about the distribution of the data and inappropriate tests could lead to incorrect statistical evaluation. One of the most commonly used tests was the (Student's) t-test as it could be easily performed and could be used when data were paired or unpaired. This test however required that the data was normally distributed which was the term used to describe a 'Gaussian distribution'. This meant that the data was symmetrically presented and the frequency of values above and below the arithmetic mean was equally distributed. If data was not 'normally distributed' it had a non-Gaussian distribution and a non-parametric test such as the Mann-Whitney U-test must be used to test the significance of difference between two treatment outcomes.

Statistical analyses significance estimation

Teva submitted that statistical analyses in clinical trials were primarily used to compare the results obtained with the different study treatments and to determine whether they were of significant proportions to reach the pre-defined level of significance. In biological/medical fields the accepted certainty was at least 95%, which was described by a 'p' value of $p \leq 0.05$ but this estimation was only valid if an appropriate test had been used.

Statistical analyses of symptom-free days in Price et al

Teva submitted that the data on symptom-free days in this study were not 'normally distributed' as stated by the author. Therefore using the arithmetic mean and the standard deviation was invalid and should not be used to describe the differences between the two treatment groups and doing so would produce a misleading conclusion. Price *et al* recognised this fact and used a Mann-Whitney U-test which was a non-parametric analysis method that was more appropriate for this type of data distribution and would provide a valid result.

Review of assessment of asthma symptoms and symptom-free days

Symptom-free days

Teva submitted that symptom-free days had been developed over the last 10 years as an important patient reported outcome measure. This measure had been developed as there was a growing awareness that asthma was a wholly treatable disease with the advent of effective inhaled corticosteroids and the newer combination therapies of inhaled corticosteroids with long-acting beta-agonists. With these treatments both patients and physicians sought to reduce the burden of asthma on the lives of sufferers. This was reflected in the British Thoracic Society's Guidance on asthma. 'The aims of pharmacological management of asthma were the control of symptoms, including nocturnal symptoms and exercise-induced asthma, prevention of exacerbations and the achievement of the best possible pulmonary function, with minimal side effects'. In addition it was now well accepted that where cost effectiveness and health economic outcomes were to be assessed symptom-free days was an appropriate measure of the impact of the disease on the ability of patients to function and hence their ability to look after themselves and to work.

Patient reported outcomes were also well accepted by the regulatory authorities and both the Food and Drug Administration (FDA) and the European Medicines Evaluation Agency (EMEA) had produced guidance for companies and investigators who wished to conduct studies with these outcomes.

Teva submitted that patient reported outcomes were also accepted in the scientific community and the International Society for Pharmacoeconomics and Outcomes Research was formed 10 years ago and hosted several meetings each year to discuss and evaluate improvements in methodology. In this year's European Conference in Dublin (October 2007) a session was dedicated to present and discuss the perspective of the European Medicines Evaluation Agency and this session focussed on three major points that were included in the EMEA guidance.

Firstly, studies should be a minimum of 3-6 months' duration and longer if possible. This did not include run-in periods as the shorter studies were often confounded as patients would perceive an efficacy effect with a change in therapy, which could alter the patients' perception of the level of their disability due to the occurrence of symptoms.

Secondly, it was stated that asthma was one of the most appropriate diseases in which to use patient reported outcomes as an outcome measure as it was a chronic disease with a relatively low mortality rate. However care should be taken to ensure that the study was conducted over long-enough periods to ensure that seasonal differences and episodic exacerbations did not bias the results.

Thirdly, it was reinforced that if patient reported outcomes were to be used as an endpoint, then it was important to select an appropriate sample size that was supported by earlier studies that might include Phase II work.

Teva submitted that there was considerable support for the view that if a patient reported outcome was to be measured such as quality of life and symptom-free days the study should be longer than 6 months and preferably one year in duration.

Symptom-free days had now been used for many years as a measure of asthma therapy effectiveness and for the analysis of cost effectiveness (Malone *et al* 2003, Price *et al*) and Teva had provided a list of 199 studies which referred to symptom-free days 127 of which included this as an outcome measure. The studies included the commonly used medicines including Seretide, Symbicort, budesonisde, ciclesonide and many other medicines. Symptom-free days were therefore a commonly used and well accepted end point for analyses in clinical studies.

Asthma symptoms vs. symptom-free days

Teva submitted that the assessment of symptom-free days must not be confused with traditional assessment of listed symptoms. Historically, asthma studies had recorded the occurrence and severity of symptoms that were related to asthma, and analysed them in the traditional way. Often there were few differences as the studies were inadequately powered for this measure and their relevance was often questioned. If a patient was treated for asthma the most important question to them was whether they felt well and could function in the normal way. A measure of this was now accepted to be measured by health related quality of life questionnaires and assessments of symptom-free days.

Teva submitted that Price *et al* defined a symptom-free day as 'an absence of wheeze, cough, shortness of breath and chest tightness in one day, including overnight'. This was very different from the occurrence of asthma symptoms and this was easily illustrated. A patient might report that they suffered from 6 symptoms in a week and these might include 3 attacks of wheeze that required use of their reliever medication (short acting beta agonists), one episode of tightness of the chest, one episode of shortness of breath and one episode of cough. This could give the impression that this patient was very unwell and it could indicate that on 6 days a patient could have experienced a symptom that impaired their ability to function. Equally, it could also be the case that a patient suffered from 6 symptoms that were caused by three attacks of wheeze on one day and that the patient remained well for the remaining six days during the week. This would be considered to be an acceptable result by both physician and patient.

Teva submitted that in Fireman *et al* and Price *et al* the symptom-free days results were clearly defined and were used as a measure of effectiveness of the two test products in accordance with usual practice and formed the basis of the cost-effectiveness analysis. This was appropriate, conformed to current guidelines and showed a clear benefit for Qvar compared with CFC-BDP.

Teva submitted that symptom-free days and asthma symptoms measured and assessed different established outcomes. The results were neither comparable nor interchangeable, but both were defined and accepted by the major regulatory authorities in Europe and North America.

Review of the clinical studies contained in the Panel ruling

Teva noted that in the Panel ruling four clinical studies were evaluated (Gross *et al*, Davies *et al*, Magnussen *et al*, Fireman *et al* and Price *et al*) but key differences between them had been ignored by Trinity-Chiesi despite this being the subject of several letters to the company. 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). Teva submitted that studies could only be compared if they were comparable in these evaluations and in this case it was clear that this was not so.

Study selection

Teva submitted that of the four studies in the discussion only Gross *et al* and Fireman *et al* and Price *et al* presented statements relating to use of symptom-free days. Davies *et al* and Magnussen *et al* did not measure symptom-free days. Therefore as this complaint was based on the interpretation of symptom-free days and as this measure was totally different from an analysis of individual symptoms, these studies should be disregarded from the ruling and were irrelevant to this appeal.

Teva submitted that of the studies described above only Fireman *et al* and Price *et al* provided any data concerning symptom-free days. Gross *et al* claimed that there were no differences between the groups but presented no data to support this statement and in the absence of any data indicating the values and 95% confidence intervals this statement must be interpreted with extreme caution. Conversely Fireman *et al* and Price *et al* presented full data on the median values of the symptom-free days and the 95% confidence intervals and as the study was conducted over 12 months the conclusions were robust. Teva submitted that in a recent discussion with Professor Price he had fully supported this conclusion. Fireman *et al* and Price *et al* presented full data and there were twice as many symptom-free days in Qvar patients compared with those receiving CFC-BDP as defined by appropriate non-parametric statistical methodology.

Objectives

Teva noted that the objective of Gross *et al* was to confirm if '[due to] improved lung deposition of [CFC-free BDP] in comparison to CFC-BDP … lower doses of [CFC-free BDP] may be required to provide adequate asthma control'. The primary endpoint variable was 'morning peak expiratory flow over weeks 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.

Teva noted that 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 [pressurised metered dose inhaler] to therapy with [Qvar] 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 peak expiratory flow (am and pm), forced expiratory volume over 1 second, daily asthma symptoms and number of times beta agonists were used, were recorded.

Teva noted that the objective of Price *et al* was 'To compare the cost effectiveness of … 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 and drug-only direct healthcare costs'.

Sample size

Teva noted that in Gross *et al*, a total of 113, 117 and 117 patients were enrolled into the three treatment groups of CFC- free BDP, CFC-BFD and CFC-free placebo respectively.

Teva noted that Fireman *et al* and Price *et al* had a total 473 of which 350 patients received CFC- free BDP and 118 (intention-to-treat (ITT) analysis) patients received CFC-BDP. Therefore, as Fireman *et al* contained a much larger sample size, it had a significantly greater statistical power than Gross *et al* so it was not surprising that Fireman *et al* could detect differences which Gross *et al* could not.

Teva submitted when evaluating a study it was usual practice to enrol enough patients in to a study to ensure that any conclusion was robust and could withstand scrutiny. In the 1980s and 1990s 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 it became common practice to determine sample size that was required based on previous pilot studies, which although were too small to provide a reliable conclusion provided an assessment of the likely difference in outcomes that would be encountered in conducting 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.

Study design and study medication

Teva submitted that 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.

Run-in period

Teva submitted that oral steroids modified the symptoms in asthma and this difference alone could make these studies incomparable. Gross *et al* treated all patients with 30mg oral prednisolone for 7-12 days and demonstrated reversibility of asthma symptoms as assessed by at least 15% increase of am PEFR. In a striking contrast, patients in Fireman *et al* and Price *et al* were not allowed to have any steroids for 30 days before entry into the study. This was a major difference between the two studies and symptom assessments after 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. Conversely, Fireman *et al* and Price *et al* 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.

Teva therefore submitted that these studies were not comparable and it was inappropriate to make the value judgements listed in the Trinity-Chiesi complaint and the Panel ruling.

Study Duration

Teva noted that Fireman et al, Price *et al* and Gross *et al* had very different study durations.

- Gross *et al* was conducted with a 10-12 day run-in period followed by 12 weeks' treatment with study medicine.
- Fireman *et al* and Price *et al* were conducted for a 12 month period with no oral steroid run-in period.

Study Medication

Teva noted that in Gross *et al* patients were randomised to receive either CFC- free BDP at 400mcg/day or CFC-BDP 800mcg/day following the 7-12 day oral steroid therapy. This medication schedule was biased in favour of the CFC-BDP and as the patients had uncontrolled asthma as defined by the fact that they had experienced symptoms in the last 5 days of the run-in period, the dose of CFC- free BDP was lower than that licensed for use in the UK. The Qvar SPC stated that a 2:1 dose ratio of Qvar to CFC-BDP was licensed for use in controlled patients and patients with uncontrolled asthma should change to Qvar at a 1:1 dose compared with CFC-BDP. This was a major confounding factor in this study design and medication selection. Conversely, Fireman *et al* and Price *et al* only admitted patients whose asthma was controlled 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

Teva submitted that the most fundamental difference between these studies was that the patients in each differed significantly in degree of the control of their symptoms before enrolment. These differences alone might already account for any changes seen later in the study.

Teva submitted that 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]' (emphasis added). Gross *et al* defined asthma symptoms as a mean morning peak expiratory flow between 50% and 80% of predicted normal value plus one of the following: sleep disturbance on ≥1 nights; presence of 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 months' history of asthma (and stable symptoms for the past month) were enrolled' (emphasis added).

Teva submitted that the patient populations were therefore not comparable in many ways. This was an important difference and now there was 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.

Detailed analysis and discussion relating to each of the points raised in the ruling and how these relate to the clinical manuscripts and conclusions

Teva submitted that Fireman *et al* and Price *et al* were much more representative of the patient types seen in general practice and the different patient types used compared to Gross et al made it impossible to obtain useful data by comparing the studies. Fireman *et al* conducted the study over a 12 month period and provided data analysed correctly by non-parametric statistical methods and presented it in a robust and correct manner. The results showed that patients treated with CFC- free BDP experienced 42.4% of symptom-free days (median; 95% CI of 32.1-57.9) whilst those treated with CFC-BDP experienced only a 20.0% (median; 95% CI of 3.8-37.9). These differences were highly significant with a p value of p=0.006. Therefore patients receiving Qvar experienced twice as many symptom-free days than those receiving CFC-BDP and this difference was highly significant.

Teva submitted other studies included by Trinity-Chiesi in its complaint provided no data concerning symptom-free days and in two of the studies symptom-free days were not measured. Individual asthma symptoms were a different outcome from symptom-free days and could not be interchanged. These studies of Gross *et al*, Magnussen *et al* and Davies *et al* could not therefore provide any useful data or contribute to the discussion of symptom free days and therefore the complaint was without merit.

Teva submitted that even if the symptom-free days had been measured the studies used short-term designs that did not comply with current guidelines for duration of studies reporting patient reported outcomes, enrolled different patient populations and 2/3 of the studies used large doses of oral steroids in the initial run-in phase. Additionally the numbers of patient in these studies were also too small to reliably detect any change in symptom-free days so it was not surprising that Gross *et al*, which claimed to assess them, failed to find a difference. These studies were claimed to be 'key studies' by Trinity-Chiesi which clearly they were not and were simply misrepresented in the complaint.

Therefore Teva submitted that the claim 'Twice as many symptom-free days' was clear and factually accurate and the study that presented data on this endpoint was well designed, conducted at the correct dose for controlled patients, with an appropriate duration that was in compliance with current guidelines and presented a valid statistical analysis.

Teva submitted that the data was thus correct, was fair and balanced and there were no relevant studies that contradicted this finding in relation to the endpoint of symptom-free days.

Review of possible mechanisms of how Qvar provided greater efficacy than CFC-BDP which resulted in twice as many symptom-free days and the possible interpretation by the prescriber.

Teva submitted that this was in keeping with known attributes of Qvar which had a small particle size which resulted in greater lung deposition than CFC-BDP. The presence of extra-fine particles resulting in increased lung deposition provided Qvar with increased efficacy which was why it was used at a lower dose than CFC-BDP in controlled patients with an efficacy ratio of 2:1 (Qvar to CFC-BDP). Therefore a physician would take from these data that Qvar was more potent than CFC-BDP and therefore it was not surprising that Qvar was associated with an improved outcome of patients with an increase in symptom-free days. In addition these findings were entirely consistent with the quality of life assessments published for the same study by Juniper *et al* (2002) which also demonstrated benefit for patients receiving Qvar.

The fact that patients received benefit from Qvar over and above that seen by CFC-BDP was therefore correct.

Teva did not agree with the conclusion that the claim 'Twice as many symptom-free days contravened Clause 7.2.

COMMENTS FROM TRINITY-CHIESI

Trinity-Chiesi stated that the vast majority of Teva's appeal went into details that were not relevant to the central issue which was did the claim of 'Twice as many symptom-free days' in its current form breach Clause 7.2, ie 'Information, claims and comparisons must be accurate, balanced, fair, objective, unambiguous and must be based on an up to date evaluation of all the evidence and reflect that evidence clearly …'? Trinity-Chiesi alleged that this claim was in breach of Clause 7.2.

Trinity-Chiesi noted Teva had stated that the whole process had become very drawn out and one feature had been the way in which Trinity-Chiesi had written a very large number of letters in which it continually changed the basis of its complaint, and Teva had provided robust answers to all of them. Additionally, Teva had noted that some of the comments in the ruling appeared to be inconsistent and could be considered either incorrect or misleading. Trinity-Chiesi stated that its responses to Teva and the Panel were within the required timeframe of ten working days. The volume of correspondence sent to Teva reflected the changing Qvar promotional campaigns from the 'Think small – make a big difference – opportunity to do more' campaign with a Bonsai tree to the 'Doing more for patients' campaign with the beach holiday scene. The letter from the Panel detailing its ruling was dated 19 October and Teva's subsequent appeal was dated 16 November 2007 which was significantly beyond the ten working days from when an appeal must be lodged. Furthermore, since the Panel ruling, journal advertisements stating this claim had continued to appear regularly in various journals including Pulse and The Pharmaceutical Journal.

Trinity-Chiesi noted that Teva was particularly concerned that there appeared to be little acceptance or acknowledgement that the recording of individual symptoms, which included wheeze, cough, shortness of breach and chest tightness, were not interchangeable with the recording of symptom-free days and that they measured different outcomes. Trinity-Chiesi did not suggest that the parameter of symptom-free days was interchangeable with asthma symptoms however, the data on asthma symptoms in Fireman *et al* should be discussed alongside the 'symptom-free days' data as it was very relevant to the recipient of Qvar promotion and provided prescribers with a greater understanding of the outcomes related to asthma symptoms in this study when considering using Qvar. Without this information the claim was unbalanced and potentially misleading.

With regard to Teva's view that the studies listed in the complaint were not comparable and did not provide any relevant data relating to the incidence of symptom-free days in the different treatment groups, Trinity-Chiesi stated it was not for Teva to decide whether a study that has assessed symptom-free days was relevant to health professionals. Teva was obliged to reflect and/or discuss all the evidence in a fair and balanced manner and allow health professionals to draw their own conclusions on whether Gross *et al* was relevant to their practice. As stated above, data on asthma symptoms was of relevance to prescribers when discussing symptom-free days particularly as the same four asthma symptoms were assessed in all three of these studies (Gross *et al*, Davies *et al* and Magnussen *et al*) as well as in Fireman *et al*.

In response to Teva's view that the Panel's ruling

would have major implications on the way research-based companies could interpret data which would put such companies at a disadvantage to companies that conducted minimal research and then tried to invalidate extensive studies of competitor companies and which, as in this case, demonstrated benefit to patients in a pragmatic real-life setting, Trinity-Chiesi stated that 3M as a research-based company clearly conducted a number of trials on Qvar before selling on the marketing and distribution rights. Chiesi was also a research-based company and would equally be concerned should the above suggestion be substantive, however, this was a deliberate distraction from the central issue which was, did the claim 'Twice as many symptom-free days' in its current form breach Clause 7.2? As stated above, Teva had an obligation to reflect and/or discuss all the evidence in a fair and balanced manner and allow the health professionals to draw their own conclusions on whether the data reflected a pragmatic life setting in contrast to other studies that had assessed symptom-free days and asthma symptoms in a controlled environment.

In response to Teva's submission that the claim 'Twice as many symptom-free days' had been used since 2004 without complaint from a health professional or another company, Trinity-Chiesi stated that the fact that Teva had not received any complaints previously was irrelevant and did not support the notion that the claim was therefore acceptable. It should be noted that during that time no other company was actively promoting a CFC-BDP or CFC-free BDP metered dose inhalers and Teva's claims were most probably much less scrutinised.

In response to Teva's submission that the Panel had provided a detailed analysis of several studies that claimed to demonstrate different outcomes but these were incorrectly categorised in the initial complaint and that despite several letters Trinity-Chiesi had continued to misrepresent these studies, Trinity-Chiesi noted that Teva had specifically clarified this minor oversight (Gross *et al* – described as a blinded study whereas Davies *et al* and Magnussen *et al* were described as double-blind, double dummy studies) in its response to the complaint. It was Trinity-Chiesi's understanding that the Panel was aware of this oversight before it considered the matter and ruled the claim in breach of Clause 7.2.

Trinity-Chiesi stated that Teva's discussion around the statistics was a deliberate distraction and peripheral to the central issue which was, did the claim 'Twice as many symptom-free days' in its current form represent all the relevant available evidence?

Trinity-Chiesi noted that in Teva's response to the complaint it described Price *et al* (published in Pharmcoeconomics) as a refereed, vetted, prestigious, widely read journal and suggested that consequently the published information should be accepted as being correct. Similarly, Gross *et al* was published in Chest, which Trinity-Chiesi considered to be an equally highly respected respiratory journal. However, Teva's appeal had speculatively challenged the foundations of this study substantially which contrasted with Teva's previous viewpoint on Price *et al*.

The lung function parameters measured in Gross *et al*, Davies *et al*, Magnussen *et al* and Fireman *et al* could not support the claim that Qvar provided greater efficacy than CFC-BDP at comparable licensed doses.

Trinity-Chiesi reaffirmed its position that the claim 'Twice as many symptom-free days' was in breach of Clause 7.2.

APPEAL BOARD RULING

The Appeal Board noted that the claim 'Twice as many symptom-free days' was referenced to Price *et al* which was a pharmacoeconomic study based on the clinical results of Fireman *et al*.

Fireman *et al* evaluated whether asthma patients with symptoms controlled with CFC-BDP could be switched to CFC-free BDP at half the CFC-BDP dose without, *inter alia*, adversely affecting the control of asthma symptoms. Throughout the one year study patients recorded their daily asthma symptoms (wheeze, cough, shortness of breath and chest tightness) on a scale of 0 to 5 and the number of times they used a reliever inhaler. The authors recorded that there were no consistent differences between the treatment groups with regard to individual asthma symptoms or daily use of reliever inhalers. Both groups recorded an increase in percentage of symptom-free days between baseline and one year (CFC-BDP 4.6% vs CFC-free BDP 11.5%). The authors concluded that asthma control was maintained in both groups.

Based on the clinical data generated by Fireman *et al*, Price *et al* compared the cost effectiveness of CFC-free BDP with CFC-BDP. Price *et al* assessed asthma symptoms in terms of symptom-free days which was a composite end point defined as the absence of all of the following: wheeze, cough, shortness of breath and chest tightness, in one day (including overnight). A table of data recorded the percentage symptom-free days and showed at baseline the median percentage symptom-free days in the CFC-free BDP group was 21.4% [95% confidence interval 14.3-28.6] and in the CFC-BDP group it was 12.7% [6.7-28.6] (p=0.226), ie there was almost a two fold difference between the groups at baseline. This difference was maintained throughout the study such that after one year the median percentage symptom-free days in the CFC-free BDP group was 42.4% [32.1 – 57.9] and 20% [3.8 – 37.9] in the CFC-BDP group. The Appeal Board noted that the confidence intervals overlapped. It was this data which formed the basis of the claim 'Twice as many symptom free days'.

The Appeal Board did not consider that Price *et al* was sufficiently robust as to support the claim 'Twice as many symptom free days'. The data had been derived from a pharmacoeconomic evaluation of primary clinical data in which no difference between CFC-free BDP and CFC-BDP in terms of asthma control had been shown. There was no indication in Price *et al* to show that the study had been powered to detect a statistical difference in percentage symptom-free days;

there had, in any case, been a two-fold difference between the two treatment groups at baseline in this regard, a difference which was present at the end of the study. The Appeal Board considered that given the data on which it was based the claim at issue was misleading and upheld the Panel's ruling of a breach of Clause 7.2. The appeal was unsuccessful.

Complaint received	**31 May 2007**
Case completed	**9 January 2008**

CASE AUTH/2008/6/07

MEMBER OF THE PUBLIC/DIRECTOR v PROSTRAKAN

Breach of undertaking and promotion of Rectogesic

A member of the public complained about the promotion of Rectogesic (glyceryl trinitrate (GTN) rectal ointment) by ProStrakan. As the complaint involved three allegations of a breach of the undertaking given in Case AUTH/1892/9/06, these were taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings.

The complainant noted that four months after being told of the outcome of Case AUTH/1892/9/06, he had found a number of Internet sites containing ProStrakan press releases dated 23 March 2006 and 27 September 2006 and two sites containing the ProStrakan Annual Report. All of the documents contained the misleading statement regarding the properties and licensed indication for Rectogesic which was the subject of the ruling in Case AUTH/1892/9/06 namely 'Rectogesic works by relaxing the vascular smooth muscle around the anal canal leading to the dilation of peripheral arteries and veins, aiding the healing of the fissure'. Bearing in mind how easy it was to find these sites, had the company attempted to identify and withdraw these pieces? If not, why not?

The complainant had also found, on ProStrakan's website, a press release which was attached to the company's preliminary financial results for the year ended 31 December 2005 and the company's annual report and accounts 2005. Both of these contained the offending misleading statement regarding the non-existent healing properties of Rectogesic. There was no reason why the company could not have easily identified these and removed them from its website; not to have done so demonstrated a disregard for the Authority which bordered on contempt.

The Panel noted that the Rectogesic summary of product characteristics (SPC) stated that the therapeutic indication was 'relief of pain associated with chronic anal fissure'. The SPC gave a pharmacodynamic explanation as to the effect of GTN ointment via the release of nitric oxide and how this might heal anal fissures but nonetheless clearly stated that in three studies the healing of anal fissures in patients treated with Rectogesic was not statistically different from placebo. Further that Rectogesic was not indicated for healing of chronic anal fissure. Rectogesic was only licensed for the relief of pain associated with chronic anal fissure. In Case AUTH/1892/9/06 the Panel had considered that the claim that Rectogesic aided 'the healing of fissures' was inconsistent with the SPC and thus inaccurate. Breaches of the Code were ruled and on 9 November 2006 the company gave its undertaking in acceptance of those rulings.

The complainant had now found a number of Internet sites containing press releases, or an annual report, which pre-dated Case AUTH/1892/9/06. The Panel considered that it was unreasonable to expect a company to be responsible for every independent site on the Internet which contained information about its activities or products as reported by third parties. This was historical recording of data in electronic form and was beyond the company's control. In that regard the Panel considered that ProStrakan had not breached its undertaking. No breach was ruled which was appealed by the complainant. The Panel considered that material posted on a company's own website was different to that above and that, where possible, it should be amended, or withdrawn, in the light of adverse rulings under the Code. The company had amended the 27 September 2006 press release as this was not an official reporting requirement. It was most unfortunate that the information in the annual report was inconsistent with the SPC but the Panel accepted ProStrakan's explanation that some official documents, once published, could not be changed. The 2005 annual report and accounts and the company's 2006 financial results for the year ended 31 December 2005 had to stay on ProStrakan's site in their original form. In that regard the Panel considered that ProStrakan had not breached its undertaking. No breach of the Code was ruled together with no breach of Clause 2. These rulings were appealed by the complainant.

The Appeal Board was concerned that claims ruled in breach of the Code remained published on independent third party sites on the Internet. Nonetheless the Appeal Board considered that it was unreasonable to expect a company to be responsible for independent sites on the Internet which contained information about its activities or products as reported by third parties. The Internet was a dynamic ever changing medium and third party, independent sites with which a company had had no direct contact, were beyond a company's control. The Appeal Board upheld the Panel's ruling of no breach of the undertaking. The appeal on this point was unsuccessful.

The Appeal Board considered that material posted on a company's own website was different to that above and that, where ever possible, it should be amended, or withdrawn, pursuant to the provision of an undertaking. The company had amended the 27 September 2006 press release as this was not an

official reporting requirement. It was most unfortunate that the information in the annual report was inconsistent with the SPC however the Appeal Board accepted ProStrakan's explanation that some official documents, once published, could not be changed. The 2005 annual report and accounts and the company's 2006 financial results for the year ended 31 December 2005 had to stay on the ProStrakan site in their original form; in any event, to have amended them by way of a note of explanation, as suggested by the complainant, would have amounted to a corrective statement which was not a sanction imposed upon ProStrakan in Case AUTH/1892/9/06. The Appeal Board considered that ProStrakan had not breached its undertaking. The Appeal Board upheld the Panel's ruling of no breach of the Code including Clause 2. The appeal on these points were unsuccessful.

The complainant further noted that his search had identified an 'Advertisement Feature' on the electronic version of Pulse which the complainant alleged promoted Rectogesic. The article dealt with the treatment of anal fissures using 'Licensed topical GTN 4mg/g' which, to the complainant's knowledge, could only be Rectogesic. The article was sponsored by ProStrakan and bore the company logo. It was a two-sided piece and included another advertisement for Rectogesic.

The first treatment algorithm recommended a further 6-8 weeks treatment with Rectogesic if the first course of treatment was not completely successful. This was contrary to the licensed indication that 'Treatment may be continued until the pain abates, up to a maximum of 8 weeks'. The algorithm also suggested that, if after an initial course the patient was unhealed and asymptomatic then the treatment should be continued for a further 6-8 weeks. Asymptomatic patients did not suffer pain. Rectogesic was only licensed for the treatment of pain, not healing, and therefore this too represented another breach of the Code.

The Rectogesic advertisement also did not have any prescribing information. The date of preparation was January 2007. This meant that when this advertisement feature was prepared, the company was aware of the decision regarding the misleading nature of its statement about the non-existent healing properties of Rectogesic, yet it still went ahead with it. Did this not represent yet another breach of the undertaking given in Case AUTH/1892/9/06?

The Panel noted that the complainant had referred to a Quick Guide article which had been developed for publication in The Practitioner journal (December 2006) but had also, unbeknown to ProStrakan, appeared on the online Pulse site. The Quick Guide, headed 'Advertisement Feature', was entitled 'Management of chronic anal fissure' and had been sponsored by ProStrakan.

The Panel noted that one of the objectives in developing the Quick Guide was to maintain Rectogesic's position as the number one treatment for anal fissures. The Quick Guide did not refer to Rectogesic per se but two treatment algorithms noted that topical glyceryl trinitrate 4mg/g was the only licensed medicine. A half page abbreviated advertisement for Rectogesic appeared at the end of the Quick Guide. The Quick Guide was headed 'Advertisement Feature'. It had been developed in association with ProStrakan which had paid for it to be produced. The Panel considered that the article promoted Rectogesic and that the company's involvement in its development, together with the placement of an advertisement, meant that ProStrakan was responsible for its content.

As prescribing information for Rectogesic was not included a breach of the Code was ruled. The Panel did not consider that the last half page of the Quick Guide was a discreet and wholly separate abbreviated advertisement; the whole of the two pages was a full advertisement which lacked prescribing information. It was not an abbreviated advertisement, and thus no breach was ruled in that regard.

The Quick Guide featured a treatment algorithm. For patients with recurrent uncomplicated anal fissures or those who had first presented with idiopathic anal fissure one of the first-line treatments was stated to be topical GTN 4mg/g (ie Rectogesic) for 6-8 weeks. If patients remained unhealed and asymptomatic or if there was some improvement in their condition, a further treatment course of 6-8 weeks was recommended. The Panel noted, however that the Rectogesic SPC stated that treatment might be continued until the pain abated, up to a maximum of 8 weeks. The SPC further stated that if anal pain persisted, differential diagnosis might be required to exclude other causes of pain. In the Panel's view the recommendation to repeat the 6-8 weeks treatment course was inconsistent with the SPC in breach of the Code.

The Panel further noted that a second treatment period of 6-8 weeks was advocated in patients who were unhealed and asymptomatic. Such patients by definition would not have pain and as such were not suitable to be treated with Rectogesic. The algorithm was thus inconsistent with the SPC. A further breach of the Code was ruled.

The Panel considered that although the treatment algorithm was different to material previously considered in Case AUTH/1892/9/06 it nonetheless advocated the use of Rectogesic in patients with anal fissure but no pain ie for healing. In that regard the Panel considered that the Quick Guide was caught by the previous undertaking and thus the undertaking had been breached. A breach of the Code was ruled.

The Panel noted that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in the future. It was very important for the reputation of the industry that companies complied with undertakings. The undertaking in Case AUTH/1892/9/06 was signed on 9

November 2006 ie two weeks before the printer's deadline and four weeks before the last date on which the Quick Guide could have been pulled. The Panel considered that the company's failure to stop the publication of the Quick Guide meant that ProStrakan had brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

A member of the public complained about the promotion of Rectogesic (glyceryl trinitrate (GTN) rectal ointment) by ProStrakan Group Plc. As the complaint involved three allegations of a breach of undertaking these were taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings.

1 Press release and annual report

COMPLAINT

The complainant alleged that ProStrakan had breached its undertaking with regard to Case AUTH/1892/9/06. He was told of the outcome of the case at the beginning of January 2007. Having waited a reasonable time (4 months) in order to allow the company to make arrangements to comply with the decision, the complainant conducted his own, very rudimentary check by typing 'ProStrakan, Rectogesic and "Healing of the fissure"' into a search engine and was directed to the following:

- 6 sites containing a ProStrakan press release dated 23 March 2006 and entitled: 'ProStrakan Group plc, the European specialty pharmaceutical company today announces its preliminary results for the year ended 31 December 2005'.

- 5 sites containing a ProStrakan press release dated 27 September 2006 and entitled: 'ProStrakan announces US$ 9 million (£4.7 Million) outright purchase of worldwide rights to Tostran and Rectogesic'.

- 2 sites containing the ProStrakan Annual Report 2005.

All of these contained the misleading statement regarding the properties and licensed indication for Rectogesic which was the subject of the ruling in Case AUTH/1892/9/06 namely 'Rectogesic works by relaxing the vascular smooth muscle around the anal canal leading to the dilation of peripheral arteries and veins, aiding the healing of the fissure'.

ProStrakan would no doubt claim that this was unfortunate but that the company could have little influence over the content of these sites. This might, or might not, be true. However, bearing in mind how easy it was, to quickly and easily find these sites, had the company no doubt with vastly more IT resources at its disposal, attempted to identify and withdraw these pieces? If not, why not?

The complainant was interested to hear the Authority's decision regarding all of the above but in particular he noted that his simple search which led him to two documents on ProStrakan's website ie: a press release which was attached to the company's preliminary financial results for the year ended 31 December 2005 and the company's annual report and accounts 2005.

Both of these still contained the offending misleading statement regarding the non-existent healing properties of Rectogesic. There was no reason why the company could not have easily identified these and removed them from its website. Indeed, not to have done so demonstrated a disregard for the Authority which bordered on contempt. Therefore, in these instances, the complainant believed that the breaches of undertaking were clear.

When writing to ProStrakan, the Authority asked it to respond in relation to Clauses 2 and 22 of the Code.

RESPONSE

ProStrakan stated that it was very concerned about the nature of this complaint, the anonymity allowed the complainant to repeatedly attack the organisation without any declaration of conflicts of interest. ProStrakan refuted the suggestion that its activities disrespected the Authority, in addition, as an organisation ProStrakan could not be held responsible for the historical recording of material on the Internet, which was an unreasonable expectation of the complainant. ProStrakan included copies of all press related materials since the ruling last year, which clearly showed its compliance with the letter and spirit of the Code. ProStrakan therefore considered that it had not breached its undertaking.

The two electronic communications mentioned by the complainant from March 2006 and the 2005 annual report were indeed posted in ProStrakan's archive as the company was obliged under the Financial Service Authority's Disclosure and Transparency Rules applicable to listed companies. The Annual Report and financial statements had to remain on the website for five years following publication. ProStrakan was unable to amend them as they were official documents. Following the complaint last year ProStrakan amended the 27 September press release, as this was not an official reporting requirement.

PANEL RULING

The Panel noted that the Rectogesic summary of product characteristics (SPC) stated that the therapeutic indication was 'relief of pain associated with chronic anal fissure'. Section 5.1 of the SPC gave a pharmacodynamic explanation as to the effect of GTN ointment via the release of nitric oxide and how this might heal anal fissures but nonetheless clearly stated that in three studies the healing of anal fissures in patients treated with Rectogesic was not statistically different from placebo. Further that Rectogesic was not indicated for healing of chronic anal fissure. Rectogesic was only licensed for the relief of pain associated with chronic anal fissure. In Case AUTH/1892/9/06 the Panel had considered that the claim that Rectogesic aided 'the healing of fissures' was inconsistent with the

particulars listed in the SPC and thus inaccurate in that regard. Breaches of the Code were ruled and on 9 November 2006 the company gave its undertaking in acceptance of those rulings.

The complainant had now found a number of sites on the Internet containing press releases, or an annual report, which pre-dated Case AUTH/1892/9/06. The Panel considered that it was unreasonable to expect a company to be responsible for every independent site on the Internet which contained information about its activities or products as reported by third parties. This was historical recording of data in electronic form and was beyond the company's control. In that regard the Panel considered that ProStrakan had not breached its undertaking. No breach of Clause 22 was ruled. The Panel considered that material posted on a company's own website was different to that above and that, where possible, it should be amended, or withdrawn, in the light of adverse rulings under the Code. The company had amended the 27 September 2006 press release as this was not an official reporting requirement. It was most unfortunate that the information in the annual report was inconsistent with the SPC however the Panel accepted ProStrakan's explanation that some official documents, once published, could not be changed. The 2005 annual report and accounts and the company's 2006 financial results for the year ended 31 December 2005 had to stay on the ProStrakan site in their original form. In that regard the Panel considered that ProStrakan had not breached its undertaking. No breach of Clause 22 was ruled together with no breach of Clause 2. These rulings were appealed by the complainant.

APPEAL BY THE COMPLAINANT

The complainant noted he had first complained about a misleading statement in the press relating to Rectogesic almost two years ago. ProStrakan had stated at the time that it was not responsible for the statement and had not been responsible for misleading the press. The Panel decided that it had to take the company's word for this and found in its favour. However the complainant had subsequently demonstrated that ProStrakan had produced misleading materials for the press; the company was found in breach of the Code and obliged to sign an undertaking that it would, amongst other things, ensure that all possible steps would be taken to avoid a similar breach of the Code in the future. It was not disputed that, despite this ruling, a number of pieces of material containing misleading information about Rectogesic continued to be available, and therefore presumably read, on independent sites on the Internet. ProStrakan had stated that as an organisation it could not be held responsible for the historical recording of material on the Internet, which was an unreasonable expectation of the complainant. The Panel agreed with ProStrakan and ruled that it was unreasonable to expect a company to be responsible for every independent site on the Internet which contained information about its activities or products as reported by third parties. This was historical recording of data in electronic form and was beyond the company's control. In that regard the Panel considered that ProStrakan had not breached its undertaking.

The complainant disagreed very strongly with the decision. Firstly, both the Panel and ProStrakan described this as an historical recording. Well, of course, it was, and it was considerably more historic now than it was at the time of the original ruling last year but this was surely a result of the Panel's and ProStrakan's tardiness in dealing with the matter. Was the Panel implying that the longer a company could get away with disseminating misleading information on the Internet, the less likely it was to be called to account for it?

The complainant noted that the Panel had considered that it was unreasonable to expect a company to be responsible for every independent site on the Internet. This rather overstated how onerous the task would be in this particular case, in that the complainant identified very few sites. It was surely not beyond the wit and resources of an organisation the size of ProStrakan to write to each of these six sites to at least request them to take down the misleading material or at least inform them of the misleading nature of the material and of the decision of the Panel. This principle was covered in the Guidelines on company procedure relating to the Code of Practice, paragraph 11, Breaches of the Code, which stated 'Procedures must be in place to ensure that promotional material found to be in breach of the Code is quickly and entirely withdrawn from use, not forgetting material stored electronically and/or in the hands of others such as printers and agencies'. One might not consider press releases to be promotional material but it was surely not too much to expect that the same principle should apply to them.

However, even if there were more than six sites identified, the complainant alleged that this should not abrogate ProStrakan of its responsibility to do whatever it could to stop continually misleading the public. All of these sites contained information which was derived from material produced by the company specifically for this purpose, and distributed to the press in order to enhance sales of its products or increase its share price or both. Presumably the misleading information would have contributed to such an effect and, as long as it continued to be read, continued to do so. Such information produced by the company would presumably have been sent to various media outlets, agencies and individuals in the first place. Therefore, presumably it should be equally possible for the company to contact all these same organisations and individuals to advise them of the Panel's ruling and request cessation of use of the misleading materials, ie it should be no more or less complicated than disseminating the misleading material in the first place. Also the question of how arduous or otherwise this task was, was surely irrelevant in that a sanction should surely reflect and counteract any benefit which the company had obtained, and continued to obtain, from its offence. The knowledge that it would be required to make efforts to fully rectify the effects of any misleading materials which they produced would surely help to make companies more careful about the information about themselves and their products which they

disseminated to the public through press releases etc. The continued presence of this unqualified misleading ProStrakan material in the public domain might rather cast doubt over the effectiveness and deterrence of the sanctions available to the Panel (the complainant referred to the 2005 House of Commons Health Committee report into the Influence of the Pharmaceutical Industry [paragraphs 360 and recommendation number 23]). One was still prompted to ask whether any company would decide that the convenient availability of widespread and misleading information on the Internet, which could lead to increased use and sales of its products, was worth the relatively minor cost of an administrative charge. The complainant stated that he had asked in his original complaint (five months ago now) if the Panel could also let him know how much ProStrakan previously had to pay as administrative charges for its breaches of Clauses 9.1 and 20.2 (Case AUTH/1892/9/06). The complainant had not received a response to this request and asked to be provided with one.

In summary, the complainant did not think that it was unreasonable to expect ProStrakan to have at least tried to have this material withdrawn and that not to have made any attempts at all to do so represented a breach of undertaking.

The complainant stated that with regard to the alleged breach of undertaking relating to materials on the ProStrakan website his response on this matter was similar to the one above. The main thrust of ProStrakan's defence and the Panel's ruling appeared to be that there was a conflict between its obligations to the financial regulators and those to the Panel. If it was indeed true that financial regulations precluded its removing or amending the misleading materials, then surely there was nothing to prevent it adding new and separate materials to its website warning readers that the offending materials contained misleading statements about its products and explaining the Panel's ruling. Not to do so meant that the financial community which read these documents would be misled as to the nature of ProStrakan's products and therefore possibly the company's value. The financial regulators would surely not be happy with this state of affairs – it might be worth discussing this with them.

The complainant alleged that the statement in ProStrakan's undertaking which obliged it to take all possible steps to avoid a similar breach of the Code in the future had not been fulfilled and he wished to appeal the Panel's ruling of no breach of Clauses 2 and 22.

Finally, the complainant noted that ProStrakan had again objected to his anonymity. Over the past two years the complainant noted that his complaints about ProStrakan had resulted in at least six rulings of breaches of the Code, including bringing the industry into disrepute. These were serious matters about which the Panel would not have been aware had the complainant not brought attention to them. Removal of the right to anonymity might be helpful for companies such as ProStrakan in that it might reduce scrutiny of them, but it certainly would not be helpful to patients, doctors, the financial community or the public and the complainant therefore hoped that the Panel were not considering ProStrakan's request.

COMMENTS FROM PROSTRAKAN

ProStrakan submitted that it had maintained its original position and agreed with the decision of the Panel that as an organisation it could not be held responsible for the historical recording of material on the Internet which was an unreasonable expectation of the complainant. The Panel commented in its ruling that it was unreasonable to expect a company to be responsible for every independent site on the Internet which contained information about its activities or products as reported by third parties. ProStrakan submitted that there were many prescription medicines that could be typed into the Internet which led to independent sites containing unsubstantiable claims for which the parent company could not be held responsible or be expected to remove, eg medicines for erectile dysfunction and weight loss. This was a widespread issue and not specific to ProStrakan.

ProStrakan included a quotation from the PMCPA website below:

'Press releases about a medicine do not require prescribing information, although it is considered good practice to include a summary of product characteristics. Once a press release is issued, however, a company should have no control over the placement of any subsequent article and nor should it, or its agent, make any payment in relation to an article's publication. Where articles appear in the press should be at the publisher's discretion and articles should be printed wholly at the publisher's expense. If a company, or its agent, controls or in any way pays for the placement of an article about a product, then that article will be regarded as an advertisement for the product'.

ProStrakan submitted that as it had no control over the independent websites quoted by the complainant, or paid for placement on them, then surely it could not be held accountable for information posted on them. It was a wholly unreasonable request for ProStrakan, or any company for that matter, to have control over what was posted on the world wide web.

With regard to the alleged breach of undertaking relating to materials on the ProStrakan website, ProStrakan maintained its original position in that it was indeed a legal obligation not to amend any financial statements or annual reports and so it was unreasonable, following the Panel's ruling, for the complainant to expect it to do so.

ProStrakan noted that the two electronic documents cited by the complainant from March 2006 and the 2005 annual report were indeed posted in its archive, as it was obliged under the Financial Service Authority's Disclosure and Transparency Rules applicable to listed companies. The annual report and financial statements had to remain on its website for five years from publication. ProStrakan was unable to amend them as they were official documents.

Following the complaint last year ProStrakan had amended the 27 September press release, as this was not an official reporting requirement.

ProStrakan noted that the complainant again made an extended point of insisting on maintaining his anonymity. ProStrakan did not understand his motivation for remaining anonymous as it had no benefit to his complaints and again did not reveal any potential conflicts of interest. ProStrakan strongly objected to this and insisted the complainant revealed his identity as it was now in a position that looked like a sustained personal attack on ProStrakan which, following the Panel's ruling, could be of no further benefit to doctors or patients. ProStrakan questioned the motivation of this complainant. ProStrakan would also ask how many other organisations had this complainant launched a sustained process of complaints against over their claims or independent website listings?

ProStrakan respected the authority of the Panel and always made every effort to work within the letter and spirit of the Code. ProStrakan had signed the undertaking to the Panel's ruling and complied with the Panel's decisions.

COMMENTS FROM THE COMPLAINANT

The complainant noted that ProStrakan appeared to believe that the presence of misleading information on the Internet was none of its responsibility. The truth was that it was entirely ProStrakan's responsibility as it produced and distributed the press releases which resulted in this widespread misinformation in the first place. It was not unreasonable to expect ProStrakan to expend at least as much effort and resource to correct these misleading statements as it expended in creating and disseminating them in the first place. That ProStrakan appeared to have done nothing at all in this respect was a disgraceful abrogation of responsibility and further brought the industry into disrepute. If the ABPI and the PMCPA were unwilling or powerless to compel pharmaceutical companies to do anything at all to at least try and correct misleading and factually incorrect statements about their products which they managed, by hook or by crook, to get onto the Internet, then the complainant feared that the authority and reputation of both organisations would be seriously undermined. The complainant stated that he had asked about the size of the administrative fees paid by ProStrakan so far so as to contrast these paltry amounts with the potentially enormous profits it stood to gain from increased sales and share prices which could result from the kind of misinformation which it had been repeatedly peddling.

The complainant noted that once again ProStrakan objected to his anonymity and asked why the company was so concerned to know his identity? How could knowing his identity mitigate any of its proven and accepted disgraceful behaviour? ProStrakan was sadly mistaken if it thought that by knowing his identity it could intimidate him into silence. The complainant reminded ProStrakan that he had brought to the attention of the Panel and the public serious matters concerning its track record of continuing disregard for the facts and regulations, such as to result in judgements that it had failed to maintain high standards, breached undertakings to its own regulatory body and brought discredit to, and reduced confidence in, its industry. The complainant was proud of his achievements in this respect and he thought ProStrakan should spend its time looking closely at the way it ran its business and question its own behaviour, ethics and motives rather than his.

APPEAL BOARD RULING

The Appeal Board noted that Rectogesic was indicated for 'relief of pain associated with chronic anal fissure'. The Appeal Board noted the company's submission about the steps it had taken to comply with the undertaking given in Case AUTH/1892/9/06.

The Appeal Board was concerned that claims ruled in breach of the Code remained published on independent third party sites on the Internet. Nonetheless the Appeal Board considered that it was unreasonable to expect a company to be responsible for independent sites on the Internet which contained information about its activities or products as reported by third parties. The Internet was a dynamic ever changing medium and third party, independent sites with which a company had had no direct contact, were beyond a company's control. In that regard the Panel considered that ProStrakan had not breached its undertaking. The Appeal Board upheld the Panel's ruling of no breach of Clause 22. The appeal on this point was unsuccessful.

The Appeal Board considered that material posted on a company's own website was different to that above and that, where ever possible, it should be amended, or withdrawn, pursuant to the provision of an undertaking. The company had amended the 27 September 2006 press release as this was not an official reporting requirement. It was most unfortunate that the information in the annual report was inconsistent with the SPC however the Appeal Board accepted ProStrakan's explanation that some official documents, once published, could not be changed. The 2005 annual report and accounts and the company's 2006 financial results for the year ended 31 December 2005 had to stay on the ProStrakan site in their original form; in any event, to have amended them by way of a note of explanation, as suggested by the complainant, would have amounted to a corrective statement which was not a sanction imposed upon ProStrakan in Case AUTH/1892/9/06. The Appeal Board considered that ProStrakan had not breached its undertaking. The Appeal Board upheld the Panel's ruling of no breach of Clause 22 and consequently Clause 2. The appeal on these points were unsuccessful.

2 Quick Guide 'Advertisement Feature'

COMPLAINT

The complainant further noted that his Internet search had identified an 'Advertisement Feature' on the

electronic version of Pulse which the complainant alleged promoted Rectogesic. The article dealt with the treatment of anal fissures using 'Licensed topical GTN 4mg/g' which, to the complainant's knowledge, could only be Rectogesic. The article was sponsored by ProStrakan and bore the company logo. It was a two-sided piece and the bottom half of the second side contained another advertisement for Rectogesic. The article bore the reference MO11/141 and the Rectogesic advertisement had a 'date of preparation' and the reference MO11/129 included within it. Were these dates and reference numbers inserted by the publishers or by ProStrakan? If ProStrakan was responsible then the complainant concluded that both pieces were prepared and presumably approved by ProStrakan for use in this way.

The complainant alleged that the 'Advertisement Feature' was an advertisement for Rectogesic which did not include prescribing information in breach of Clause 4.1.

The first treatment algorithm contained a recommendation for a further 6-8 weeks treatment with Rectogesic if the first course of treatment was not completely successful. This was contrary to the licensed indication which stated 'Treatment may be continued until the pain abates, up to a maximum of 8 weeks'. A breach of Clause 3.2 was alleged.

This same algorithm also suggested that, if after an initial course of treatment, the patient was unhealed and asymptomatic then the treatment should be continued for a further 6-8 weeks. Asymptomatic patients did not suffer pain. Recotgesic was only licensed for the treatment of pain, not healing; a further breach of Clause 3.2 was alleged.

The Rectogesic advertisement also did not have any prescribing information. The complainant noted that prescribing information was not required on an abbreviated advertisement. He was not clear what an abbreviated advertisement was but noted from Clause 5.2 that such advertisements were not allowed on the Internet. Thus he suspected that this advertisement breached either Clause 4.1 or 5.2 or both. Also he saw that the date of preparation was January 2007. This meant that when this advertisement feature was prepared, the company was aware of the decision regarding the misleading nature of its statement about the non-existent healing properties of Rectogesic, yet it still went ahead with it. Did this not represent yet another breach of undertaking relating to the decision on Case AUTH/1892/9/06?

When writing to ProStrakan, the Authority asked it to respond in relation to Clauses 2 and 22 of the Code in addition to the clauses cited by the complainant.

RESPONSE

ProStrakan explained that the advertisement feature was designed to highlight the steps involved in managing chronic anal fissures. It was not an advertisement for Rectogesic and clearly discussed all of the therapies in this area, in a balanced and informed way. There was clear mention of the spontaneous healing rate of chronic anal fissures independent of therapy. In addition, there was clear mention that topical therapies only aided the management of pain.

ProStrakan noted the allegation of a breach of Clause 4.1 but submitted that as the Quick Guide was not an advertisement there was no requirement for prescribing information and no breach of Clause 4.1.

The complainant had further alleged that the mention in the first algorithm of a second course of topical therapy was a breach of Clause 3.2 and that asymptomatic patients were treated a further breach. As stated above this was not an advertisement for Rectogesic and therefore not in breach.

For clarification topical treatments for chronic anal fissure were used for 6-8 weeks of continuous treatment, this did not preclude a physician prescribing a second separate course of 6-8 weeks. This advertisement was intended for health professionals, presumably as the complainant was not treating patients with this very painful condition he was unaware of this. In addition, the complainant had been selective in his interpretation of the algorithm regarding further treatments. The option referred to actually stated, 'Unhealed and asymptomatic or some improvement' (emphasis added). In such circumstances patients could still be symptomatic and as such health professionals used their judgement to decide appropriate courses of action.

The advertisement was an abbreviated advertisement for the printed version of Pulse, it was not an Internet advertisement and as such was not in breach of the alleged clause.

In response to a request for further information ProStrakan stated that it was shocked to discover that the advertisement feature and the abbreviated advertisement still appeared on the Pulse website and immediately contacted the publishers to re-request that the piece be removed. ProStrakan had never commissioned the item to be placed on the website and did not pay for it to appear there; its contract was exclusively for a bound insert in Practitioner. The company was never told by the publishers that the item was to be placed on the electronic version of Pulse. ProStrakan was extremely concerned this was done entirely without its knowledge and had taken steps to ensure that the publishers never initiated any publishing in any media in future without signed consent.

ProStrakan paid for the generation of the article, (a copy of the proposal from the publishers was provided) to be published as a Quick Guide to be bound in Practitioner. The items at issue were produced to replace the run-on when the product name was changed to comply with European legislation from Rectogesic 0.4% to Rectogesic 4mg/g. The publishing agreement, as enclosed, included placement of the Rectogesic advertisement within the article.

ProStrakan stated that the printer's deadline was 24

November 2006. Printed documents were finally bound on 8 December 2006. If the company had pulled the item the last available date would have been a couple of days before final binding.

ProStrakan stressed that this truly was an exceptional situation and it maintained robust policies and procedures to comply with the Code, which were regularly reviewed and updated. The company was very disappointed that the actions of a publisher, which were completely outside its control, had resulted in this complaint.

PANEL RULING

The Panel noted that the complainant had referred to a Quick Guide article which had been published on the Internet. The Quick Guide had been developed for publication in The Practitioner journal (December 2006) but had also, unbeknown to ProStrakan, appeared on the online Pulse site. The Quick Guide, headed 'Advertisement Feature', was entitled 'Management of chronic anal fissure' and had been sponsored by ProStrakan. The last half page of the two page Quick Guide was taken up with an advertisement for Rectogesic.

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 contents, 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 noted that a document from the publishers stated that one of the objectives in developing the Quick Guide was to maintain Rectogesic's position as the number one treatment for anal fissures. The Quick Guide itself did not refer to Rectogesic per se but two treatment algorithms noted that topical glyceryl trinitrate 4mg/g was the only licensed medicine. A half page abbreviated advertisement for Rectogesic appeared at the end of the Quick Guide. The Quick Guide was headed 'advertisement feature'. It had been developed in association with ProStrakan and ProStrakan had paid for it to be produced. The first page and a half included a reference code MO11/141 and the advertisement part of the Quick Guide had a reference code MO11/129. Taking all the circumstances into account the Panel considered that the article was promotional for Rectogesic. The Panel considered that the company's involvement in the development of the article, together with the placement of an advertisement, meant that ProStrakan was responsible for the content of the Quick Guide under the Code.

The Panel noted that the Quick Guide had, unbeknown to ProStrakan, been published on the Internet. Although this was not at the behest of ProStrakan the company was nonetheless responsible for what its agents did on its behalf.

The Panel considered that the Quick Guide was, in effect, promotional material for Rectogesic which should have thus included prescribing information for the product. No prescribing information was included and so the Panel ruled a breach of Clause 4.1 of the Code. This ruling was accepted by ProStrakan. The Panel did not consider that the last half page of the Quick Guide was a discreet and wholly separate abbreviated advertisement; the whole of the two pages was a full advertisement which lacked prescribing information. Thus although the article included a visual which appeared to be an abbreviated advertisement, and it had appeared on the Internet, no breach of Clause 5.2 was ruled.

The Quick Guide featured a treatment algorithm for primary care. For patients with recurrent uncomplicated anal fissures or those who had first presented with idiopathic anal fissure one of the first-line treatments was stated to be topical GTN 4mg/g (ie Rectogesic) for 6-8 weeks. If patients remained unhealed and asymptomatic or if there was some improvement in their condition, a further treatment course of 6-8 weeks was recommended. The Panel noted, however that the Rectogesic SPC stated that treatment might be continued until the pain abated, up to a maximum of 8 weeks. It was further stated in the SPC that if anal pain persisted, differential diagnosis might be required to exclude other causes of pain. In the Panel's view the recommendation to repeat the 6-8 weeks treatment course was inconsistent with the particulars listed in the SPC. A breach of Clause 3.2 was ruled.

The Panel further noted that a second treatment period of 6-8 weeks was advocated in patients who were unhealed and asymptomatic. Such patients by definition would not have pain and as such were not suitable to be treated with Rectogesic which was only indicated for relief of pain associated with chronic anal fissure; Rectogesic was not indicated for healing. The algorithm was thus inconsistent with the particulars listed in the SPC. A further breach of Clause 3.2 was ruled.

The Panel considered that although the treatment algorithm was different to material previously considered in Case AUTH/1892/9/06 it nonetheless advocated the use of Rectogesic in patients with anal fissure but no pain ie for healing. In that regard the Panel considered that the Quick Guide was caught by the previous undertaking and thus that the undertaking had been breached. A breach of Clause 22 was ruled.

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

complied with undertakings. The undertaking in Case AUTH/1892/9/06 was signed on 9 November 2006 ie two weeks before the deadline for getting the PDFs of the Quick Guide to the printers and four weeks before the last date on which the item could have been pulled. The Panel considered that the company's failure to stop the publication of the Quick Guide meant that ProStrakan had brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

Complaint received **6 June 2007**

Case completed **9 November 2007**

CASE AUTH/2017/7/07

ANONYMOUS REPRESENTATIVES v TEVA

Asthma review service

The complainant stated that as a current member of Teva's sales force (s)he was concerned about how representatives were encouraged to achieve their targets for Qvar.

Representatives were asked to sign surgeries up to an asthma review service (the Enhanced Asthma Care Service) provided by an agency, which in turn would find patients suitable to be changed to Qvar. The service was supposed to help practices review their asthma patients and be non-promotional but representatives were increasingly pressurised to sign up at least of six surgeries per year. It was a big issue if representatives fell behind these targets or if the form did not specify a switch to Qvar or Qvar Easi-Breathe.

If the service was purely meant to benefit the practice only, why would the company make such a big deal of setting minimum targets for each representative? The complainant considered the unnecessary pressure coming from the top was being passed on to the customers who might be pushed unethically into something they did not want, by people whose jobs might be at risk if they did not achieve the minimum target.

The Panel noted that supplementary information on switch and therapy review programmes, stated, *inter alia*, that the Code prohibited switch services paid for or facilitated directly or indirectly by a pharmaceutical company whereby a patient's medicine was simply changed to another without clinical assessment. Companies could promote a simple switch from one product to another but not assist in its implementation.

The Panel noted that the complainant was anonymous and noncontactable and thus was cautious when deciding how much weight to attribute to his/her evidence.

The Panel noted from training materials provided by Teva that the objective of the service was to facilitate the systematic identification and review of asthmatic patients in line with BTS/SIGN Guidelines in general practice. The service strategy and rationale in the training pack referred to sub-optimally controlled patients and it was thought that as many as 50% of patients were sub-optimally controlled based on the use of short acting bronchodilators. Teva had decided to sponsor a nurse advisor team to meet this need and review patients in a structured manner. The training materials referred to the Code and clearly stated, *inter alia*, that 'Teva support of a project must NOT be dependent on the customer prescribing a Teva product. This must be neither the fact in practice not the impression given either verbally or in any document connected with the project, internal or external'. It was also noted that the Code prohibited switch services. The introduction of the service authorization form stated that 'This service is provided on the understanding that [GPs] authorizing such services do so on the basis that the services provided are in the best medical interest of their patients and that they, as [GPs], retain complete control of the service at all times'.

The Panel noted that representatives had to introduce the service during a non-promotional call using a service detail aid. The briefing material instructed the representatives to remind the doctor of their previous conversation ie the imminent phase out of Becotide and Becloforte (CFC-containing beclometasone devices. Qvar, Teva's product, was CFC-free beclometasone). It was suggested that the phase out of Becotide and Becloforte be used as the opportunity to review all asthmatics. The representative was instructed to tell the doctor that the service could help: provide a full therapeutic review of all asthmatics; identify controlled asthmatics for a straight change to a CFC-free equivalent for both metered dose inhalers and breath actuated inhalers if required and identify sub-optimally controlled patients for review through a clinic. The briefing material did not mention the BTS/SIGN guidelines. Representatives were briefed to state that the result of the service was that 'CFC transition is implemented for the practice and patient care is optimised for your asthmatic patients'. The service detail aid itself stated that one of the benefits of the service was that it could provide an effective implementation of a CFC-free transition programme. This benefit was, however, listed after other benefits which referred to clinical assessment and the BTS guidelines.

The Panel noted that with poorly controlled asthmatics were defined as those who used an agreed number of short acting bronchodilators over a 12 month period. These people would be sent a symptom questionnaire. The Panel assumed that if patients had used less than the agreed number of short acting bronchodilators over a 12 month period then they would be defined as controlled asthmatics. In this regard, however, the Panel considered that merely noting a patient's use of reliever medication was only a surrogate marker for asthma control. It was possible that some patients who did not use a lot of short acting bronchodilators were nonetheless not optimally controlled. The Panel did not consider such identification on its own constituted clinical review. The Panel noted that nurse advisors would identify all patients that satisfied the review inclusion criteria

that the representatives had discussed and agreed with the lead GP. The instructions to representatives stated that the service design could focus on either patient control and symptoms or CFC transition. The advantages included 'enables practice to complete CFC transition'. The representative's responsibilities with regard to completion of the practice mandate included confirmation of 'which ICS [inhaled corticosteroids] patients were to be reviewed – patients receiving CFC-containing or all patients'. The Panel considered there was a discrepancy within the instructions and with regard to the selection criteria for practices to be offered the service, and queried whether the primary selection criterion really was that they must have key GPs and staff who realised the importance of identifying and reviewing asthma patients who were sub-optimally controlled and should be established on a more effective therapy.

The representatives' training presentation detailed their on-going role once the practice had signed up; this was the start not the end of their role. When scheduling the first date for agency staff to attend the surgery representatives were to make sure that they could be there to *inter alia*, remind the practice of the sponsor and 'Build the relationship three ways'. The representative was to keep in regular contact with the practice. No advice was given in the presentation regarding the relevant clauses of the Code and the limited non-promotional role of the representative once the practice had signed up.

The Panel noted Teva's comments about some PCTs' approach in switching patients from CFC to CFC-free treatment without patient review. It appeared from the materials submitted that it was possible for a practice to use Teva's service for such a switch. Documentation in this regard was included in the Teva service eg the practice treatment mandate. The practice treatment mandate identified five groups of patients: Group 1 was controlled on CFC corticosteroids; Group 2 was controlled on CFC-free corticosteroids; Groups 3 and 4 were sub-optimally controlled either on CFC or CFC-free corticosteroids and Group 5 were non-responders. A template letter, headed 'EACS Immediate Medication Change', was also provided which appeared to indicate that the patient was being switched from CFC to CFC-free without clinical review. The Panel queried why such a template letter was provided at all if practices were chosen because they wanted to identify and review asthma patients who were sub-optimally controlled and establish them on a more effective therapy. A number of items in the training materials referred to the service enabling practices to complete CFC transition. The Panel noted its comments above about the discrepancy between the stated aims of the service and the training and other materials. There were no instructions about what representatives and nurse advisors were to do if all the practice required was a switch from CFC to CFC-free treatment. This was a significant omission.

The Panel had some serious concerns about the arrangements for the service in question and noted that switch services were expressly prohibited under the Code. In this regard the Panel specifically queried the representatives' role in discussing and agreeing inclusion criteria with the GP, the possible inclusion of patients controlled on CFC corticosteroid preparations and the provision of a template 'switch' letter.

In the Panel's view the representatives' briefing material contained mixed messages regarding switch programmes. On one hand representatives were reminded that switch services were prohibited, on the other they were told to 'sell' the services on the basis that, *inter alia*, prescribers could use it to identify controlled patients and do a straight change to a CFC-free beclometasone product (CFC transition appeared to be a greater priority than clinical assessment of patients); template letters for immediate medication change were provided. The Panel considered that the material for the service should have been consistent and made it abundantly clear that switch services without clinical assessment were wholly unacceptable. There should have been no room for doubt. On balance the Panel considered that the representatives' briefing material was ambiguous such that it might be seen by some as advocating a course of action which was likely to lead to a breach of the Code as alleged. In addition and on balance the arrangements for the audit as described in all of the material were unacceptable in relation to the requirements of the Code. Breaches were ruled. The Panel considered that in the conduct of the service, high standards had not been maintained. A breach of the Code was ruled. Given its rulings above the Panel also ruled a breach of Clause 2 of the Code. All but one of these rulings were appealed by Teva.

The Appeal Board acknowledged the clinical value of a review service in asthma given the number of uncontrolled patients and the imminent discontinuation of CFC corticosteroid inhalers. Very many patients even if well controlled, would soon have to be changed over from CFC- containing products to CFC-free alternatives.

The Appeal Board noted that practices were offered the service in question before representatives knew what their prescribing choices would be. In that regard the asthma review service was not linked to the prescription of any medicine. No breach of the Code was ruled.

The Appeal Board, however, noted that a section of the Practice Treatment Mandate which recorded the prescribing decision had to be completed by the Teva representative and the GP. In such circumstances the Appeal Board considered it highly likely that, where such therapy was appropriate, the GP would feel pressurised to specify Qvar. The Appeal Board considered it unacceptable for the representative to be present when the GP recorded his/her prescribing decision and in this regard upheld the Panel's ruling of a breach of the Code.

Notwithstanding its ruling of a breach of a breach of the Code, overall the Appeal Board did not consider

that high standards had not been maintained. No breach of the Code was ruled in that regard. It thus followed that there was no breach of Clause 2 of the Code.

An anonymous representative complained about the promotion of Qvar (CFC-free beclometasome) by Teva UK Limited.

COMPLAINT

The complainant stated that as a current member of Teva's sales force (s)he was concerned about a part of the business which was becoming increasingly pressurised.

The main product promoted was Qvar and representatives obviously had targets which the complainant did not have a problem with. It was how representatives were encouraged to achieve these targets that was worrying.

Representatives were asked to sign surgeries up to a non-promotional asthma review service [the Enhanced Asthma Care Service] provided by an agency, which in turn would find patients suitable to be changed to Qvar. As this was a service that was supposed to help practices review their asthma patients and be non-promotional, it was of concern that representatives were increasingly pressurised to sign up at least of six surgeries per year, which was clearly stated in the representative's mandate. It was a big issue if representatives fell behind these targets or if the form did not clearly specify a switch to Qvar or Qvar Easi-Breathe.

If the service was purely meant to benefit the practice only, why would the company make such a big deal of setting minimum targets to be achieved by each representative? The complainant considered the unnecessary pressure coming from the top was being passed on to the customers who might be pushed unethically into something they did not want, by people whose jobs might be at risk if they did not achieve the minimum target.

The representative stated that (s)he had had to submit this complaint anonymously for fear of reprisal, but (s)he was sure that plenty of evidence would be found in emails, representative mandates etc.

When writing to Teva, the Authority asked it to respond in relation to Clauses 2, 9.1, 15.9, 18.1 and 18.4 of the Code.

RESPONSE

Teva was very surprised and concerned that an employee had complained to the Authority as it had a detailed whistleblower policy which helped and supported employees to alert management to any activities and behaviours they considered improper or unethical. The process was non-judgemental and anonymous. Amongst others it covered a course of conduct which seemed improper for behaviour in Teva or which might compromise or embarrass the representative or Teva, if it were known by co-workers or the public.

The whistleblower policy also stated that an individual should 'Remember that failure to report a violation of the Code is in itself a violation'. Therefore the complainant had failed to follow company procedures.

With regard to this anonymous complaint which suggested increasing pressure in relation to their daily roles and expectations, Teva's response would demonstrate that as a responsible employer it provided objectives 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 explained that all employees including sales teams within the pharmaceutical industry were set targets on a number of parameters; including non-sales related activities and therefore it was not unreasonable to set a target in relation to the Enhanced Asthma Care Service. Each representative was required to achieve a baseline of six service implementations per year based on the finite resource. This would ensure that the service was both conducted by nurses that lived throughout the UK and was evenly available to GP surgeries in all regions. It was not unreasonable to expect that targets set for completion in any given year were tracked against performance of all employees within Teva. The sales force was no exception to this.

Teva also noted that as discussed below, the demand for the service outstripped supply and so it was hard to understand the foundation of the complainant's comments about falling behind targets.

Teva would also demonstrate that the service offering complied with the Code. It denied breaches of Clauses 18.4, 18.1, 15.9, 9.1, or 2. The GP practice directed and controlled the service at all times in line with the Data Protection Act 1998.

Representative mandate – meeting the requirements of Clauses 15.9 and 9.1

The mandate clearly set out the focus placed on the representative's different activities. The section on service stated '1.5x surgery referral per quarter from the Enhanced Asthma Care Service'. All relevant sections of the Code were referenced appropriately and clear guidance was outlined eg how representatives were to offer the service. Representatives were told 'Note: You must not discuss any issues relating to Enhanced Asthma Care Service within a promotional sales call. This must be done in a separate service call, on a separate occasion.'

This was a limited resource that was in demand from primary care trusts (PCTs) and health boards and as such it operated on a first come first served basis with representatives. The six per representative per year was indicative of the number each representative could expect to offer if a calculation was made on the number

of nurses employed by the agency, the number of working days in a year, the days on average that the service took to complete divided by the number of representatives.

Teva noted that as from March 2007 it had increased the size of its sales force. Another agency was also appointed to supply a dedicated contract sales team as from March 2007. All representatives had been identically trained. The calculation of the resource available for representatives to offer was based on the number of representatives on territory and the available working days from the agency nurses. Details were provided to support the target of 6 services per year per representative working from 1 January 2007.

Current demand for the service outstripped the available nurse resource, for example one health board had recommended in writing that its 100 practices undertook the service.

Teva believed that its briefing materials were appropriate, fair and clear. Teva clearly positioned the nurse service within these briefing materials as providing a service to medicine that was non-promotional.

Teva did not understand why a sales person should be worried about achieving targets as it was a key measure of any sales or commercial position in any industry.

Enhanced Asthma Care Service – meeting the requirements of Clauses 18.1 and 18.4

Service rationale and aims

Asthma was one of the most common and treatable conditions affecting patients in the UK. Asthma UK quoted the following statistics:

- 1 in 12 adults had asthma
- 1 in 10 children had asthma
- The UK had one of the highest rates of people with asthma of any country in the world
- 1,400 died of asthma each year in the UK.

Whilst the number of deaths was small compared to heart disease and cancer the difference was that it was believed that up to 90% of these deaths were preventable (Asthma UK) if practices managed patients in line with the BTS/SIGN (British Thoracic Society/Scottish Intercollegiate Guidelines Network) guidelines.

This was well recognised by opinion leaders in this area and a leading expert – a consultant chest physician and former chair of the BTS Standards of Care Committee – had stated that 'asthma can be very successfully treated by health professionals if time was applied and BTS/SIGN guidelines were followed. Asthma can be adequately controlled if a patient is prescribed the correct medicine, with an adequate management plan. Hospital admissions could be reduced and quality of life improved if patients took their treatment and were given correct advice'.

Unfortunately whilst asthma care was far from optimum as demonstrated by the above statistics its successful management was well down the list of NHS priorities and this was reflected in the fact that it was given little prominence within the GMS contract. The service had been designed to help put asthma back on the NHS agenda by raising the awareness that 'asthma is not sorted' and that the BTS/SIGN guidelines provided the framework for successful management. The service was a full BTS/SIGN implementation service that provided additional resources (specialist asthma nurses) to help deliver improved patient outcomes. The service has been requested by strategic health authorities, health boards, PCTs and many individual practices for that purpose.

For the patient the service aimed to achieve a level of asthma symptom control that allowed them to lead a normal life and to minimise exacerbations with minimal side-effects.

For the practice the service aimed to: ensure the patient received the optimum treatment in line with the practice protocol; implement interventions after review which would aim to improve patient outcomes and provide a service to patients in line with the BTS/SIGN guidelines together with the clinical governance agenda.

The service was undertaken for the benefit of the NHS and was in the best interests of the patient.

Practice recruitment and the authorization process

The service provided a full therapeutic review for the practice; it was introduced in detail to the practice by the Teva representative in a non-promotional call. In some instances the Teva representative might have delivered a brief description of the service during a promotional call and delivered the approved bridging item prior to the non-promotional call. The Teva representative was responsible for ensuring that the practice completed the authorization form.

Completion of the service authorization form

Practices interested in undertaking the service completed sections 1 and 2 of the service authorization form which included the practice treatment mandate prior to the engagement of the service provider.

The authorization form permitted the practice to define which asthmatics it wished to review and to agree a course of action to follow for each patient group at each step of the guidelines.

At least two GP signatories (ideally all partners) was required. In a single handed practice, one GP signature supported by the signature of the practice nurse or manager would be sufficient. The GP signatories stated that they were authorized to sign on behalf of the practice and undertook to accept full responsibility for communicating the activities contained therein to all members of the practice whom the service activities would affect. A lead GP for the service was nominated who would be responsible for liaising with the agency

nurse and practice staff to ensure the smooth implementation of the service.

Patients included in the asthma review

Within the authorization form the practice could decide whether to review asthma patients on all types of inhaler or just those on specific types of devices depending on practice requirements. All inhaler device types available were given on the authorization form. The lead GP for the service authorized the practice decision.

Practice treatment mandate

The service process was then discussed with the GP after which the practice completed the Practice Treatment Mandate and authorized the practice requirements.

For the purposes of service delivery patients were split into controlled and sub-optimally controlled patient groups.

Sub-optimally controlled patients were defined as those who had had an agreed number of short-acting bronchodilator (SAB) inhalers over the previous 12 month period. An over-reliance on SAB inhalers, which were used for symptomatic relief, indicated that the patient needed further investigation as recognised in the BTS/SIGN guidelines.

Patients defined by the practice as sub-optimally controlled were sent a symptom questionnaire. This established if they had experienced asthma symptoms in the last month which either affected their ability to sleep, affected them during the day or interfered with their ability to undertake normal activities.

The Practice Treatment Mandate allowed the practice to define a course of action for all possible patient groups:

- Patients on CFC containing corticosteroids who were controlled (in line with practice definitions)
- Patients on CFC containing corticosteroids who were sub-optimally controlled
- Patients on CFC free corticosteroids who were controlled
- Patients on CFC free corticosteroids who were sub-optimally controlled
- Non responders to symptom questionnaires.

This represented the majority of asthma patients, however patients on combination therapies and other additive therapies were all included in the review and presented as controlled/uncontrolled in line with the number of SABs set by the practice. Dependent on the protocol being implemented there might be both step down and step up actions being implemented by the agency nurse advisor.

The practice might decide to define a range of treatment options for each patient group which following a full therapeutic review might include being invited to a clinic, medicine changes, no action or an alternative course of action that the practice would like to follow.

All prescribing decisions for each patient group were made by the practice prior to the engagement of the agency. The agency implemented the BTS/SIGN guidelines utilising the practice protocol.

Finally, prior to contacting the agency to implement the service the lead GP signed the authorization form.

Scheduling the event

The agency had a dedicated service scheduling line which practices could call after completing the authorization form in order to book a specialist asthma nurse to implement the practice protocol. The signed authorization form was then sent to the agency for forwarding to the allocated nurse.

Service implementation stage by stage

The overall service structure was given in the service authorization form:

Service overview

The support provided by the agency following the completion of the authorization form was in three stages as detailed below. The service took approximately four days (including two clinic days) to deliver in an average three GP practice.

Service stages in detail

1 Patient identification

Agency nurse advisors identified all patients that satisfied the review inclusion criteria set by the practice in the authorization form. Following identification of the patients the nurse advisor would produce the template letter, approved by the GP at their initial meeting, to accompany the patient engagement material (including symptom questionnaire) that would be sent to all patients that satisfied the practice's inclusion criteria.

2 Patient review

Responses from the questionnaire were incorporated into a practice baseline report which would include information on all asthma patients in the practice.

Nurse advisors could not and would not discuss or recommend any specific therapy choices, but in line with their duty of care they would question GPs who appeared reluctant to fulfil their obligations to review patients who, in the nurse's professional opinion might require additional support and care.

If, after the presentation of patient summaries, the GP wished to implement any actions with any patient in order to fulfil the guidance laid down by the BTS/SIGN guidelines – for instance medicine upgrade or invitation to a consultation, the nurse advisor would implement the written instructions given by the GP

prior to leaving the practice. The GP might decide to take no action because the treatment was considered to be suitable.

The nurse advisor would also let the practice know about those patients who did not respond to the questionnaire and who might therefore require an alternative approach and those patients whose treatment fell outside of the BTS/SIGN guidelines with a recommendation that the practice bring these patients in for review.

3 Clinic review

Patients who the GP considered would benefit from a clinic review were invited to attend and counselled in accordance with the clinic mandate that the nurse advisor would discuss with the practice if a patient required step up/step down intervention.

Clinics could be carried out either by an agency nurse advisor or the practice nurse as required by the practice.

The agency nurse advisor could advise to the practice nurse on how to deliver respiratory review clinics that would be of long term benefit to the practice and their patients.

Details of what took place in the clinic were as follows:

The agency nurse advisor would advise on how the practice had decided to treat its respiratory patients. If the medicine needed to be changed as per the practice protocol, the nurse would tell the patient of the proposed new medicine and provide guidance on inhaler technique. If the patient only needed counselling this would be provided in accordance with the practice protocol.

A detailed summary sheet for each patient consultation would be presented to the lead GP. The GP would then authorize the action proposed by the agency nurse advisor in alignment with the protocol eg a medicine change or other intervention, or an acknowledgment that the patient's status was acceptable.

For all interventions authorized by the practice, the agency nurse advisor or practice nurse would update the patients' records. In addition, the patient's GMS asthma template would be updated to capture the findings of the review. A letter informing the patient of this would be produced by the nurse advisor and left with the practice for posting.

At the end of clinic days the agency nurse advisor would transmit the patient anonymised data relating to the clinic activity to the agency head office.

At the completion of the service to a practice, a report detailing respiratory patient caseload status and actions undertaken would be left with the practice. It was anticipated that the report would be of value when the practice reviewed its delivery of GMS Quality Outcome Framework key indicators and demonstrated that it had undertaken a review to improve quality of care. A sample practice report was included in the representative training folder.

A practice folder was created by the nurse advisor at the start of the service into which a constantly updated copy of the authorization form was inserted along with hard copies of signed/approved template letters, authorized course of action sheets (individual GP signatures against each patient for medicine changes) and a CD containing all search data and baseline information. This folder was the practice's permanent record of every action undertaken to implement the BTS/SIGN guidelines within the practice.

The service implemented a full therapeutic review in line with the BTS/Sign guidelines for the practice. The practice defined which patients were to be reviewed the treatment mandate for each patient at all steps of the BTS/SIGN guidelines and the practice explicitly authorized any intervention for patients that met the practice mandate.

The service used agency asthma nurse specialists to 'kick start' the patient review process and implementation of the BTS/SIGN guidelines which the practice would continue following the completion of the service. The result was that the BTS/SIGN guidelines were implemented for all asthma patients in participating practices.

Representative materials related to service delivery

All representatives recruiting practices to undertake the service were trained by the agency for at least one day at the earliest opportunity. As part of the service training the agency also briefed the representative on the ABPI guidelines in relation to the provision of added value services. A representative questionnaire together with an examination and sample answer set was included in the representative's training folder.

All materials used to promote the service to health professionals clearly stated that the service was sponsored by Teva as a service to medicine ie they carried corporate branding only. All service materials sent to patients ie questionnaires and patient letters carried corporate branding only, ie included the banner 'sponsored by Teva UK Limited as a service to medicine'. Before being sent the patient letters might be modified by the GP to meet practice requirements as long as changes requested met the Code.

Patients were sent a description of the service and could opt out if they did not want a third party review of their asthma care or if they would not like a mandated medicine change to occur.

The service introduction within the representative's folder was introduced in recognition that many PCTs advocated the 'switch' from CFC formulations to CFC-free formulations without patient review. This was not in the best interest of the patient and was not advocated by the General Practitioners in Asthma Group – it recognised that the CFC transition provided an opportunity to improve asthma care by the systematic review of patients and encouraged a

managed transition which was in the best interest of the patient. Whilst the service could be used to implement the CFC transition this briefing material was provided to advocate that a 'switch' was not what the service was about. It was the patient's asthma control that was important, just because a patient was or was not on a CFC-free aerosol did not necessarily mean that they would be controlled. Whilst practices might find that the service was a useful platform to allow them to implement a CFC transition in selected patient groups, it was the view of the agency that patients should have their asthma control assessed prior to any CFC transition and symptomatic patients reviewed through clinics. Whilst a 'switch' was being advocated by many PCTs the service advocated against 'switch' and endorsed a full therapy review be conducted prior to the course of action being decided for an individual patient.

Staff working on the service

Teva provided copies of the internal briefing material for the agency nurse advisor team. Its team was passionate about optimising asthma care and was motivated by a desire to implement the practice treatment mandates of participating practices in order to 'make a difference'.

As of 30 June all nurses working full-time on this project possessed an asthma diploma or higher qualification. Teva provided the credentials of its team by way of thumb-nail CVs. Prior to their employment at the agency many of the staff worked on PCT projects relating to respiratory medicine. Recently one of the team had won a prestigious national award in recognition of innovative work in respiratory medicine.

All the nurses undertook a thorough month's training course and were trained and validated both in the classroom and in the practice environment before being sent to a practice on their own. Nurses also had to pass a written exam to demonstrate knowledge of the service before being deployed in the field.

In addition to the initial training each team member was visited once per month and their performance assessed to ensure high quality standards were addressed.

Service reports

The practice received a completion report in relation to service outcomes as outlined in the service authorization form.

When implementing the service no patient identifiable information was removed from the practice. The only information removed from the practice was an anonymised outcome report containing statistical information relating to service implementation. Before the service started the doctor signed the service authorization in order to confirm that they had read, understood and agreed with content. This section explained that the agency complied with the Data Protection Act 1998 and followed all legislation in relation to the protection of patient confidentiality. It also stated that GPs authorizing the service did so on the basis that the services provided were in the best medical interest of their patients.

In addition, on completion of the service, the authorization form was signed by the practice. This allowed the agency to give summary data about the service to Teva; no patient identifiable information was given to the company. If the practice did not sign this section then no information about the service was sent to Teva. The authorization form stated that the agency would not disclose any personal data to any third party in any circumstances except at the written request of the GP.

Contractual remunerations

The agency was paid a flat fee per nurse deployed on the project. There were no performance related bonuses paid to the agency by Teva as a direct result of the contract.

There were no incentive schemes linked to Teva product sales included in the contract or sales force performance included in the contract.

Teva provided details of the key performance indicators included within the contract and of how the service quality was assessed.

Nurses attached to the service could earn an annual bonus related to the implementation of the therapeutic review. Details were provided

Summary of compliance with Clauses 18.1 and 18.4

Teva submitted that the facts presented below when overlaid with the comprehensive description of the service above, together with the service materials provided, demonstrated that the company had complied with Clauses 18.1 and 18.4.

Clause 18.1

- 1,400 people died unnecessarily from asthma each year
- Around 90% of these deaths were preventable by better patient management
- This was well recognised by opinion leaders in this area one of whom had stated that 'asthma could be very successfully treated by health professionals if time was applied and BTS/SIGN guidelines were followed'
- The service was a full BTS/SIGN implementation service
- GPs authorizing the service explicitly signed the service authorization form to agree that they believed the EACS service was in the best medical interests of their patients
- A national opinion leader had also stated that if the BTS/SIGN guidelines were implemented 'hospital admissions could be reduced and quality of life improved if patients took their treatment and were given correct advice'. This was clearly in the best interests of patients and the NHS
- No gift, benefit in kind or pecuniary advantage

was offered in relation to the service to health professionals as an inducement to prescribe, supply, administer, recommend or buy or sell any medicine. The fact was that GPs undertaking the service must invest practice time in order to implement it, take time to agree a practice protocol and authorize each and every step of the service together with authorizing any individual patient intervention. Practice prescribing costs might increase or decrease depending on individual practice treatment mandates. Practices within their treatment mandate would decide which asthma patients to review and a course of action for each individual patient which might or might not include medical interventions. The service was a full BTS/SIGN implementation service which would help reduce hospital admissions, reduce exacerbations, reduce hospital admissions and might even prevent some unnecessary asthma deaths.

Clause 18.4

- As outlined above GPs authorizing the service explicitly signed the service authorization form to agree that they believed the service was in the best medical interests of their patients
- A national opinion leader had stated that if the BTS/SIGN guidelines were implemented 'hospital admissions could be reduced and quality of life improved if patients took their treatment and were given correct advice'. This was clearly in the best interests of patients and the NHS
- The service contained corporate branding and was clearly displayed on all service materials used with health professionals and/or practice administrative staff
- The involvement of Teva in the therapy review service was made clear to all patients. All patient engagement materials clearly stated that the service was sponsored by Teva, a pharmaceutical company which manufactured medicines for the treatment of asthma. In addition all letters sent to patients contained the same banner. Finally patients reviewed by agency nurse advisors through clinics signed the clinic assessment sheet (contained within the service authorization form) giving their expressed consent for the nurse from an outside agency to review their asthma medicine and current management
- The service was discussed in detail by the Teva representative with practices that had expressed interest in a non-promotional call. In some instance the representative would leave the service bridging piece/leavepiece about the service in a promotional call but would not instigate a detailed discussion of the service at that time
- The service provider was a sponsored registered nurse who held an asthma diploma or a higher qualification. All nurses received training in relation to the Code and the Data Protection Act 1998 as part of their initial training course before they undertook any practice activity
- No patient identifiable information was provided to Teva or any of its representatives as part of service delivery
- The nurse team was not involved in the promotion of a product in any way. The recommendation or promotion of a product by any agency nurse would constitute a breach of Teva's disciplinary process and if proven would result in gross misconduct and instant dismissal
- Contractual payments in relation to payment for the service were not linked to sales in any way. There were no performance related payments in the contract that would be payable to the service provider. The only bonus provisions related to nurse payments and was based around interventions contained within the BTS/SIGN guidelines. The service had not been designed as an audit but rather an implementation package whereby interventions were undertaken (decided by the practice within the treatment mandate) for patients who were sub-optimally controlled (the definition of sub-optimally controlled being defined by the practice) in order to optimise patient asthma outcomes. Medical and non-medical options were defined as an intervention ie there was no direction given in favour of for example a medical intervention; patient education might provide the best outcome for a patient. The nurses simply implemented what the practice dictated
- The agency operated within the framework of the detailed written instructions contained within the nurse briefing packs. This was compiled jointly between the agency and Teva and represented the operational requirements to which the agency must deliver. This pack also contained guidelines in relation to patient confidentiality and did not advocate either directly or indirectly any course of action that would be likely to lead to a breach of the Code
- Practices contacted the agency to book the service, the agency did not contact the practice. If the agency telephoned the practice for any reason the caller stated that they were from the agency which implemented the Teva sponsored service
- The practice completed the practice treatment mandate on the service authorization form prior to the engagement of the agency. Therefore when the agency staff first entered a practice they were there to implement the treatment mandate already produced by the practice. Written updates in relation the implementation were kept current and left in a practice folder. The identity of the sponsoring company was given on the authorization form that contained the treatment mandate completed by the practice. All data removed from the practice was documented on the service authorization form and the use to which that data was put. Expressed consent was gained

from the practice for such data to be removed from the practice

- All service material was non-promotional and identified the sponsoring company. The material did not comment on any competitor to Teva.

- All service materials were certified by Teva's Code of Practice signatories.

- The service was discussed with NHS trusts, health authorities, health boards and PCTs on a pro-active basis. Indeed there had been a high degree of interest and many organisations had recognised that the treatment of their asthma patients was sub-optimal. This had resulted in some organisations recommending the service to all of its practices. A BTS/SIGN guidelines service was likely to be cost neutral in relation to budgetary implications. Budgetary savings might be made in relation to hospital admissions that were in the best interest of the NHS

- The service was not a 'switch' service. The service was a full therapeutic review that assisted practices by conducting a clinical assessment of their patients and implementing the practices treatment mandate in line with the BTS/SIGN guidelines.

The service did not change patients' medicine without a clinical assessment.

Outcomes following the therapy review for individual patients might be/and were: no change; change of medicine/ device; stop medicine; change dose; patient education or addition of a spacer device.

The practice decided which interventions it believed were most appropriate for each individual patient and were documented as such. Medical and non-medical interventions were included and the product choice was not limited to those of Teva. All service documentation capturing individual interventions was left with the practice following completion of the service.

Representative mandate – meeting the requirements of Clause 9.1

Pharmaceutical sales teams were set targets on a number of parameters, including non-sales related activities; therefore it was not unreasonable to set a target in relation to the service. The target of six/representatives/year was appropriate as detailed above. It was not unreasonable to expect that targets were tracked against performance.

Teva noted that some PCTs independently recommended the service as they clearly saw the benefit to GP practices and patients alike.

The service - meeting the requirements of Clause 9.1

The practice treatment mandate was filled in by the GP authorized to do so. The practice controlled all prescribing decisions, authorizing individual medicine changes if required. The GP therefore made all decisions relating to the prescription of medicine and Teva had no input into this process. The practice was in complete control of the whole process, any decision the practice made would be implemented under the remit of the service by the agency nurse advisor.

Representative mandate – meeting the requirements of Clauses 9.1 and 2

In relation to the setting of targets, Teva noted its comments above

Teva emphasised the following in relation to the complainant's comment on '…unethically pushed…'. The practice treatment mandate was filled in by the GP or GPs authorized to do so. The practice controlled all prescribing decisions, authorizing individual medicine changes if required. The practice was in complete control of the whole process, any decision the practice made would be implemented under the remit of the service by the agency nurse advisor.

Teva believed this was a valuable independent nurse-led service that was widely accepted by doctors and primary care organizations. Teva did not believe that any health professional would sign up to the service if they did not think it was in the best interests of the practice and its asthma patients.

Internal procedures – meeting the requirements of Clauses 9.1 and 2

Teva and any contracted third party suppliers had extensive policies and procedures in place regarding grievance and business ethics. The quotes below came directly from Teva's Code of conduct.

'For Teva, it is very important to succeed, but in a single way: honestly and fairly, both from the standpoint of work relations between employees within the company and in its relations with external customers, suppliers and shareholders. The ethical behavior and integrity of Teva's people worldwide have always been an integral part of Teva's culture – the Teva Way.'

This encompassed, *inter alia*, conduct which:

- in the employee's knowledge or opinion, was illegal

- contradicted the guidelines set out in Teva's Code of Business Conduct and/or contradicted company policies and procedures

- seemed improper for behavior in Teva

- might compromise or embarrass the employee or Teva, if it were known by co-workers or the public.

It went on to explain the 'Whistleblower' procedure put in place to assist and support employees who believed that Teva's Code of Conduct might have been breached. It explained, *inter alia*, that:

- The role of Teva's audit committee in regard to the whistleblower procedures was to examine complaints and suspicions and, when necessary, to investigate

- When reporting anonymously through the 'confidential hotline', sufficient details should be provided to enable examination of the complaint (such as dates, description of events etc)

- Protection of employees – the audit committee would not reveal the identity of the person who had made the report and would not tolerate any retaliation against anyone who reported irregularities

- Those found to be in violation of this Code were subject to appropriate disciplinary action, up to and including termination of employment. Criminal misconduct might be referred to the appropriate legal authorities for prosecution.

All Teva employees attended a human resources workshop or completed an online presentation on business ethics during 2006. This was part of the induction process for all new employees.

The sales agency as a contracted third party sales force supplier also had clear guidelines on business ethics. All employees received a copy of the business ethics leaflet with their contract of employment and any employees who were with the agency at the end of 2006 also received a copy. There was a slide on business ethics and the reporting process at the company induction.

Teva and the agency had appropriate internal procedures in place to deal with complaints of this nature. Neither company had received an internal complaint via either of Teva's clearly defined anonymous internal complaint procedures on this matter from a current employee.

Additional Information

Training

Representative training ABPI – meeting the requirements of Clauses 15.9 and 9.1

All representatives were, *inter alia*, provided with a copy of the Code on their initial training courses. They had returned signed declarations that they had received and had read and understood their obligations under the Code.

The representative mandates referred to these documents appropriately.

Representative training and audit– meeting the requirements of Clauses 15.9 and 9.1
All representatives were trained on the agency nurse service offering and had a copy of the training manual and were checked on their competence to implement the service.

All training materials had been appropriately certified in line with Clause 15.9.

PANEL RULING

The Panel noted that the supplementary information to Clause 18.4, Switch and Therapy Review Programmes, stated, *inter alia*, that Clauses 18.1 and 18.4 prohibited switch services paid for or facilitated directly or indirectly by a pharmaceutical company whereby a patient's medicine was simply changed to another without clinical assessment. Companies could promote a simple switch from one product to another but not assist in the implementation of it.

The Panel noted the complainant's comments. The Panel also noted that the complainant was anonymous and noncontactable and thus was cautious when deciding how much weight to attribute to his/her evidence.

The Panel noted that Teva had provided the training materials for the representatives and for the agency nurse advisors. The material stated that the objective of the service in question was to provide GPs with a facilitation platform for the systematic identification and review of asthmatic patients in line with BTS/SIGN Guidelines. The service strategy and rationale in the training pack referred to sub-otimally controlled patients and it was thought that as many as 50% of patients were sub-optimally controlled based on the use of short acting bronchodilators. Teva had decided to sponsor a nurse advisor team to meet this need and review patients in a structured manner. The training materials referred to Clauses 18.1 and 18.4 of the Code and clearly stated, *inter alia*, that 'Teva support of a project must NOT be dependent on the customer prescribing a Teva product. This must be neither the fact in practice not the impression given either verbally or in any document connected with the project, internal or external'. It was also noted that Clause 18.4 of the Code prohibited switch services. Section 3A of the service authorization form stated in its introduction that 'This service is provided on the understanding that [GPs] authorizing such services do so on the basis that the services provided are in the best medical interest of their patients and that they, as [GPs], retain complete control of the service at all times'.

The Panel noted that representatives had to introduce the service during a non-promotional call using a service detail aid. The briefing material instructed the representatives to remind the doctor of their previous conversation ie the imminent phase out of Becotide and Becloforte (CFC-containing beclometasone devices. Qvar, Teva's product was CFC-free beclomethasone). It was suggested that the phase out of Becotide and Becloforte be used as the opportunity to review all asthmatics. The representative was instructed to tell the doctor that the service could help him: provide a full therapeutic review of all asthmatics; identify controlled asthmatics for a straight change to a CFC-free equivalent for both metered dose inhalers and breath actuated inhalers if required and identify sub-optimally controlled patients for review through a

clinic. The briefing material did not mention the BTS/SIGN guidelines. Representatives were briefed to state that the result of the service was that 'CFC transition is implemented for the practice and patient care is optimised for your asthmatic patients'. The service detail aid itself stated that one of the benefits of the service was that it could provide an effective implementation of a CFC-free transition programme. This benefit was, however, listed after other benefits which referred to clinical assessment and the BTS guidelines.

The Panel noted that with regard to patient identification, poorly controlled asthmatics were defined as those who used an agreed number of short acting bronchodilators over a 12 month period. These people would be sent a symptom questionnaire. The Panel assumed that if patients had used less than the agreed number of short acting bronchodilators over a 12 month period then they would be defined as controlled asthmatics. In this regard, however, the Panel considered that merely noting a patient's use of reliever medication was only a surrogate marker for asthma control. It was possible that some patients who did not use a lot of short acting bronchodilators were nonetheless not optimally controlled. The Panel did not consider such identification on its own constituted clinical review.

The Panel noted that it was stated that the nurse advisors would identify all patients that satisfied the review inclusion criteria that the representatives had discussed and agreed with the lead GP in the practice. The instructions to representatives stated that the service design could focus on either patient control and symptoms or CFC transition. The advantages included 'enables practice to complete CFC transition'. The representative's responsibilities with regard to completion of the practice mandate included confirmation of 'which ICS [inhaled corticosteroids] patients were to be reviewed – patients receiving CFC-containing or all patients'. The Panel considered there was a discrepancy within the instructions and with regard to the selection criteria for practices to be offered the service, and queried whether the primary selection criterion really was that they must have key GPs and staff who realised the importance of identifying and reviewing asthma patients who were sub-optimally controlled and should be established on a more effective therapy.

The representatives' training presentation detailed the representatives' on-going role once the practice had signed up to the programme and they were told that this was the start not the end of their role. When scheduling the first date for agency staff to attend the surgery representatives were to make sure that they could be there to *inter alia*, remind the practice of the sponsor and 'Build the relationship three ways'. The representative was to keep in regular contact with the practice. No advice was given in the presentation regarding the relevant clauses of the Code and the limited non-promotional role of the representative once the practice had signed up.

The Panel noted Teva's comments about some PCTs' approach in switching patients from CFC to CFC-free treatment without patient review. It appeared from the materials submitted that it was possible for a practice to decide to use the Teva service for such a switch. Documentation in this regard was included in the Teva service eg the practice treatment mandate. The practice treatment mandate identified five groups of patients: Group 1 was controlled on CFC corticosteroids; Group 2 was controlled on CFC-free corticosteroids; Groups 3 and 4 were sub-optimally controlled either on CFC or CFC-free corticosteroids and Group 5 were non-responders. A template letter, headed 'EACS Immediate Medication Change', was also provided which appeared to indicate that the patient was being switched from CFC to CFC-free without clinical review. The Panel queried why such a template letter was provided at all if practices were chosen because they wanted to identify and review asthma patients who were sub-optimally controlled and establish them on a more effective therapy. A number of items in the training materials referred to the service enabling practices to complete CFC transition. The Panel noted its comments above about the discrepancy between the stated aims of the service and the training and other materials. There were no instructions about what representatives and nurse advisors were to do if all the practice required was a switch from CFC to CFC-free treatment. This was a significant omission.

The Panel had some serious concerns about the arrangements for the service in question and noted that switch services were expressly prohibited under the Code. In this regard the Panel specifically queried the representatives' role in discussing and agreeing inclusion criteria with the GP, the possible inclusion of patients controlled on CFC corticosteroid preparations and the provision of a template 'switch' letter. The Panel noted the complainant's concern that representatives had to sign up six surgeries per year and that it was a 'big issue' if these targets were not met or if the form did not specify a switch to Qvar.

In the Panel's view the representatives' briefing material contained mixed messages regarding switch programmes. On one hand representatives were reminded that switch services were prohibited, on the other they were told to 'sell' the services on the basis that, *inter alia*, prescribers could use it to identify controlled patients and do a straight change to a CFC-free beclomethasone product (CFC transition appeared to be a greater priority than clinical assessment of patients); template letters for immediate medication change were provided. The Panel considered that the material for the service should have been consistent and made it abundantly clear that switch services without clinical assessment were wholly unacceptable. There should have been no room for doubt. On balance the Panel considered that the representatives' briefing material was ambiguous such that it might be seen by some as advocating a course of action which was likely to lead to a breach of the Code as alleged. In addition and on balance the arrangements for the audit as described in all of the material were unacceptable in relation to the requirements of Clauses 18.1 and 18.4. Breaches of Clauses 15.9, 18.1 and 18.4 were ruled. The Panel considered that in the conduct of the service,

high standards had not been maintained. A breach of Clause 9.1 was ruled. Given its rulings above the Panel also ruled a breach of Clause 2 of the Code. These rulings were appealed by Teva except the Panel's ruling of a breach of Clause 15.9 which was accepted.

The Panel then considered whether the circumstances were such that a formal report under Paragraph 8.2 of the Constitution and Procedure should be made to the Code of Practice Appeal Board. The Panel decided not to make such a report as there was clinical review for uncontrolled patients and some element of review to establish which patients were controlled. Some of the instructions referred to the requirements of Clauses 18.1 and 18.4 and their supplementary information.

APPEAL BY TEVA

Teva appealed the Panel's rulings of breaches of Clauses 2, 9.1, 18.1 and 18.4; it was very concerned that sections in the ruling appeared to be contradictory or inaccurate.

Teva accepted that some of the internal briefing materials could have discussed the implementation of the service in more detail and contained statements that could be misinterpreted but it did not accept that the asthma review programme was a switch programme. Teva was however conscious that as it was a very detailed and complex service and it had therefore had to submit a large volume of documents in its response which had made it an enormous task for the Panel to conduct a detailed review.

Teva noted that the Panel had not made a report to the Appeal Board under Paragraph 8.2 of the Constitution and Procedure as there was clinical review for uncontrolled patients.

Teva submitted that this was contradictory as for controlled patients the ruling stated that the Panel assumed that if patients had used less than the agreed number of short acting bronchodilators (SABs) over a 12 month period that they would be defined as controlled asthmatics. In this regard, however, the Panel considered that merely noting the patient's use of reliever medication was only a surrogate marker for asthma control. The Panel did not consider such identification on its own constituted clinical review.

An identical data set was collected as part of a full clinical assessment for all asthma patients within participating practices, ie for both controlled (defined as SAB use above an agreed level over the previous 12 months) and uncontrolled patients. This data set which could be seen within section 7 of the representative's manual comprised an additional 76 data sets (in addition to SAB use) that were collected for all patients as part of the clinical assessment and constituted the 'electronic baseline assessment'.

- Therefore the only action that was different for controlled and uncontrolled patients was that uncontrolled patients received a symptom questionnaire but controlled patients did not require one as they had a low level of SAB use (defined by the practice) and no asthma symptoms in the GP notes. If the practice wished to send all asthma patients a symptom questionnaire, then this could be stated on the authorization form and would be implemented by the agency if required.

- The 'electronic baseline assessment' was then presented to the practice. All 77 collected data sets relating to patients were then reviewed on an individual basis by the nurse and the GP in order for the GP to decide a course of action. This could clearly be seen on the authorization form. Even if a patient used a low number of reliever inhalers, if that patient had other treatment issues, eg admission to hospital with an asthma attack, then the practice might decide that the patient was not controlled and treat the patient accordingly. Reliever use was only used as an initial marker for asthma control. The use of reliever inhalers was a marker advocated by the BTS. In other words every patient received a full clinical review before the GP authorized a specific course of action and reliever use alone was not used to agree a course of action for an individual patient.

Controlled patients were therefore treated in exactly the same way as uncontrolled patients, the same data sets were collected from both groups of patients and no action was taken for any patient without a full clinical review with the GP.

Given the above, Teva asked why the Panel had ruled on controlled and uncontrolled patients in a very different manner and the reasoning given as both groups had been enrolled and reviewed by the GP by the same process? Why had the Panel viewed the service as a 'switch service'?

Actions taken in relation to sales force materials

Teva noted that the Panel, on balance, considered that the representatives' briefing material was ambiguous such that it might be seen by some as advocating a course of action which was likely to lead to a breach of the Code as alleged. Teva accepted this finding and had withdrawn all service materials from the sales force. The sales force was re-briefed (26 September) so there could be no misunderstanding that all company employees must adhere to the Code and briefing materials were being rewritten to ensure that there were no statements that could be considered as ambiguous. It was clearly stated that the service was a full asthma review service and not a switch service. The sales force materials now ensured that there was no possible ambiguity before they were re-issued.

Clauses 18.1 and 18.4

Teva submitted that in terms of the sales force materials, these were being amended as outlined above in order to comply with Clauses 18.1 and 18.4.

Enhanced Asthma Care Service

Teva disagreed that this service represented a switch service, thus ultimately breaching Clause 2 (as well as

Clauses 9.1, 18.1 and 18.4) and it therefore appealed against this ruling but it required clarification as stated above relating to controlled and uncontrolled patients to make an effective response. However, Teva understood the Panel's concerns and it had therefore taken the following immediate actions to implement changes prior to the appeal:

- Service recruitment was suspended on 25 September 2007
- All materials were withdrawn verbally from the sales force on 26 September at the re-briefing and by email on 1 October 2007
- All documents related to the service were now subject to review prior to appeal to ensure complete compliance with the Code.

Teva submitted that a large part of the Panel's ruling was based on the lack of a full clinical review for controlled patients. This was clearly factually incorrect as outlined above.

When it provided its reasons for its appeal Teva noted its regret that its request for clarification on the ruling had been refused as it would have aided it greatly in constructing its appeal. Teva submitted that the service greatly benefited the NHS and ultimately patients.

Teva reassured the Panel that it was committed to the Code and it had robust procedures in place to ensure compliance. The Panel's ruling contained statements that appeared to be factually incorrect. It appeared that sections of the ruling were based on assumptions that could not be substantiated from either the documents it submitted, or from the anonymous complaint. Furthermore Teva noted that the Panel had changed the words from how they appeared within some of its service materials within its ruling. This potentially questioned the basis of the ruling.

Teva requested that each member of the Appeal Board was provided with a full set of all the documents submitted in relation to this case together with the supporting CD. Importantly the CD contained a mock example of the data collected for individual patients as part of the review process. This had been provided previously in electronic copy only.

Complaint and ruling

Teva was very concerned about the way that such an anonymous complaint could be considered, the letter was ambiguous and contained comments that were untenable and without supporting evidence. This was not an equitable situation. It was difficult for Teva to construct an appeal as it was being asked to defend itself against events that had not occurred and against rulings for which a detailed rationale was not provided.

Teva noted that the Panel had stated in its ruling that the 'briefing material contained mixed messages' and the 'representatives' material was ambiguous'. In addition individual statements were quoted from materials (incorrectly in some instances) and single sentences were quoted in isolation from a given document and hence out of context.

Teva submitted that the Panel's ruling did not clearly define where the alleged breaches had arisen. In line with the guidance on appeals, Teva addressed the points in the order that they appeared in the ruling.

The above not withstanding, Teva addressed the following three issues in some depth as they appeared to provide the basis for the initial ruling and the alleged Clause 2 breach.

1 The Enhanced Asthma Care Service was a switch service
2 Controlled patients had not received a full clinical review
3 Provision of a 'switch letter'

1 The service was a switch service

Teva submitted that the definition of a switch service as outlined in the Code (Clause 18.4) was 'whereby a patient's medicine is simply changed to another without a clinical assessment'. The service at issue did not constitute a switch service as every asthmatic within the practice had a full clinical review consisting of 77 data sets:

Following the completion of the full clinical review the nurse presented the baseline assessment for the practice on an individual patient basis to the GP. Following review the GP made a clinical assessment and might request specific actions for individual patients which the agency nurse would implement. The service was one of the most detailed and comprehensive review services currently provided by the pharmaceutical industry. The service level was defined by the GP and might vary from practice to practice. The service was launched in March 2006 soon after the introduction of the current Code. As there were specific changes in Clause 18 relating to the provision of educational goods and services, extensive work was undertaken to ensure that the service structure fulfilled all the criteria necessary to meet the requirements of a therapeutic review as this document demonstrated.

The Panel's view of the service as a switch service was inaccurate given that each patient received a full clinical assessment before any intervention being requested/authorized by the practice.

2 Controlled patients did not receive a full clinical review (reliever use on its own did not constitute a clinical review).

Teva submitted that the major inconsistency in the ruling was that the Panel had stated that there was clinical review for uncontrolled patients and some elements of review to establish which patients were controlled. An identical data set was collected (as outlined in section 1 above) as part of a full clinical assessment for all asthma patients within participating practices ie for both controlled (defined as reliever use above an agreed level over the previous 12 months) and uncontrolled patients.

The only action that was different for controlled and uncontrolled patients was that uncontrolled patients

received a symptom questionnaire, but controlled patients did not require one, because of their low level of reliever use (defined by the practice) and no asthma symptoms in the GP notes. If the practice wished to send all asthma patients a symptom questionnaire then this could be stated on the authorization form and would be implemented by the nurse agency.

The 'electronic baseline assessment' was then presented to the practice. All 77 collected data sets relating to patients were then reviewed on an individual basis by the nurse and the GP in order for the GP to decide a course of action. Teva noted that just because a patient used a low number of reliever inhalers, that patient might have other treatment issues eg admission to hospital with an asthma attack. If so then the practice might decide that this patient was not controlled and treated the patient accordingly. The use of reliever inhalers was a marker advocated by the BTS. Therefore every patient received a full clinical review before the GP authorizing a specific course of action. Reliever use alone was not used to agree a course of action for an individual patient but rather formed part of a full clinical review.

Teva submitted that the Panel might have misunderstood that all patients whether classified as 'controlled' or 'uncontrolled' received exactly the same clinical review; it was the GP's decision as to whether specific patients or groups of patients were sent a symptom questionnaire.

Teva did not understand why the Panel did not consider that the identification on its own (reliever use) constituted a clinical review. Teva had clearly shown that all patients received a very extensive clinical review as outlined above, with SAB use being only one of 77 clinical review criteria that was collected for each patient.

Teva submitted that given that the review process was the same for controlled and uncontrolled patients it could only draw the conclusion that this met the requirements of the Code as it stated in the Panel's ruling that 'There was clinical review for the uncontrolled patients'.

3 Provision of a 'switch letter' (immediate medication change letter)

Teva stated that the Panel was incorrect to state that Teva had provided a template switch letter. Any letter (template or otherwise) that a GP wished to use was agreed and sent only after the GP had reviewed the full baseline assessment of all patients, on all 77 clinical review parameters. The letter could therefore not be deemed a 'switch' letter, which the Panel inferred as meaning that no clinical review had taken place before the letter was sent to the patient. The Panel appeared to have ruled on a document that taken out of sequence in relation to service delivery could be interpreted as a 'switch' letter.
With regard to each paragraph of the complaint, Teva noted the following:

'The complainant stated that as a current member of Teva's sales force (s)he was concerned about a part of the business which was becoming increasingly pressurised.'

Teva had an internal 'whistleblower' policy that all employees were told about on joining the company and throughout their employment. The 'alleged employee' who had complained anonymously did not follow the internal processes, and Teva was unaware that any individual felt pressurised as a direct result of being asked to recruit practices to undertake the service or they would have acted accordingly.

'The main product promoted was Qvar and representatives obviously had targets which the complainant did not have a problem with. It was how representatives were encouraged to achieve these targets that were worrying.'

Teva submitted that it had commented on this in its previous response but the allegations remained unsubstantiated.

'Representatives were asked to sign surgeries up to a non-promotional asthma review service [the Enhanced Asthma Care Service] provided by [an agency], which in turn would find patients suitable to be changed to Qvar. As this was a service that was supposed to help practices review their asthma patients and be non-promotional, it was of concern that representatives were increasingly pressurised to sign up at least six surgeries per year, which was clearly stated in the representative's mandate. It was a big issue if representatives fell behind these targets or if the form did not clearly specify a switch to Qvar or Qvar Easi-Breathe'.

Teva submitted that in terms of 'finding patients suitable for change to Qvar', this was incorrect. Practices requesting the service complete the service authorization form and specified specific patient groups that they wanted to review. Following a full clinical review these patients were then presented to the practice for the practice to decide a course of action (including no action) for each specific patient. This included a range of treatment options including non-medicinal options. The agency implemented the decision of the practice following review and acted purely as data processors under the Data Protection Act 1998. The agency could demonstrate that in many cases practices changed patients to products other than Qvar. That was their choice and would be stated on the service authorization form. It was untrue that if the authorization form did not specify a 'switch' to Qvar that this was a big issue for the representative.

The agency was an independent organisation governed by the Data Protection Act and other legislation that meant it could not pass any details contained on the authorization forms to Teva; hence Teva would be unaware if a practice completed a form in this manner. The form was not seen by any Teva management after being signed by the practice.

Each representative was required to recruit six practices in order that nursing resource could be shared in an equitable manner amongst the field force. Due to excessive demand from primary care the nursing headcount had to be increased since Teva's response to the complaint. There was a waiting list of

approximately five working weeks for practices requesting the service and being offered a date when a nurse advisor was able to commence service delivery, ie the figure of 6 practices per representative had been greatly exceeded and hence could not be viewed as a pressurised target. Demand from practices had far outstripped available nursing resource.

'If the service was purely meant to benefit the practice only, why would the company make such a big deal of setting minimum targets to be achieved by each representative? The complainant considered the unnecessary pressure coming from the top was being passed on to the customers who might be pushed unethically into something they did not want, by people whose jobs might be at risk if they did not achieve the minimum target'.

Teva noted that targets were a fact of life for many professions including representatives and doctors. Targets defined the expectation of the employer to the employee in order to create a transparent working environment. The target of six practices per representative was set to ensure that all nurse resources were fully utilised. As previously stated this target had been greatly exceeded and the representative's target had not been changed from six practices, despite the addition of a further five nurses. Given that this was the case why would it be necessary to exert unnecessary pressure from the top down if available resources were already being exceeded?

In relation to pushing practices into a service which they did not want Teva submitted the following:

- In order to request the service practices had to sign a detailed authorization form specifying their service requirements. If they did not want the service why sign up to it?
- Practices could withdraw from the service at any point either.
- Following the completion of events practices were asked to complete a questionnaire to assess the benefit of the review/clinic to patients and the benefits of the review/clinic service to the practice.

All categories were scored 0 (poor), 1 (satisfactory) or 2 (good). Teva submitted that the average score achieved across all UK practices where the service had been delivered was 2. If practices were being 'pushed unethically into something that they did not want' then the scores achieved would not represent universal satisfaction. Teva denied this allegation.

'The representative stated the (s)he had had to submit this complaint anonymously for fear of reprisal, but (s)he was sure that plenty of evidence would be found in e-mails, representative mandates etc if an investigation was launched into this matter.

Teva had re-briefed the internal whistleblower process that allowed for detailed complaints to be made anonymously. This was acted upon by senior management within the Teva organisation. As in this instant the whistleblower process was not utilised it was very difficult to investigate this anonymous complaint fully.

With regard the Panel's ruling, Teva made the following points:

'The Panel noted that the supplementary information to Clause 18.4, Switch and Therapy Review Programmes, stated, inter alia, that Clauses 18.1 and 18.4 prohibited switch services paid for or facilitated directly or indirectly by a pharmaceutical company whereby a patient's medicine was simply changed to another without a clinical assessment. Companies could promote a simple switch from one product to another but not assist in the implementation of it.'

Teva submitted that the service provided a full clinical assessment for every asthmatic in a practice. This was a requirement as within the service authorization form the GP signed to authorise the following: 'We agree for READ code searches to be done to identify patients coded for Asthma. Following the patient identification we also authorise a nurse review of such patients using miquest based extraction software'. This seemed to have been missed by the Panel. The representative folder contained a 'dummy baseline' report showing the information collected as part of the clinical assessment for all asthma patients. The full clinical review comprised the collation and presentation of 77 different pieces of information, relevant to the treatment of asthma that was presented to the GP/practice for review. Additional data sets might be captured should the practice wish to send selected patients a symptom questionnaire or invite an individual for a review through a nurse run clinic. This information was collected for each patient and combined into the practice baseline assessment which was then presented to the GP for review before any course of action was decided as outlined on the flow chart.

The service did not constitute a 'switch' as defined by Clause 18.4 as every patient received a full clinical assessment before the baseline assessment was presented to the practice. When presenting the baseline assessment every patient was discussed individually with the GP and the agency then implemented the course of action requested by the practice for any particular individual.

'The Panel noted that representatives had to introduce the service during a non-promotional call using a service detail aid. The briefing material instructed the representatives to remind the Doctor of their previous conversation ie the imminent phase out of Becotide and Becloforte (CFC-containing beclometasone devices. Qvar, Teva's product was CFC-free beclomethasone). It was suggested that the phase out of Becotide and Becloforte be used as the opportunity to review all asthmatics.'

Teva submitted that the service detail aid, as stated by the Panel, was used by the representative to introduce the service to a practice during a non-promotional call. Taking practices page by page through the service detail aid was the main method of communicating how the service worked.

The detail aid stated the following on the front cover:

- Enhanced Asthma Care Service
  - Helping you to deliver improved outcomes in asthma

- Page 2 highlighted amongst others the following statements:
  - There were over 1,400 deaths from asthma in the UK in 2002
  - As many as 90% of the deaths from asthma are avoidable
  - Asthma can be very successfully treated by health professionals if time was applied and BTS/SIGN guidelines were followed

- Page 3 stated:
  - Provides a full therapeutic review of your asthma patients

- Page 7 (practice benefits) stated:
  - Clinical assessment in accordance with BTS guidelines

From the above it should be noted that the service provided the practice with a full clinical assessment of all asthma patients irrespective of whether they were on a CFC-containing inhaler or a CFC-free inhaler. Simply because a patient was on a CFC-free inhaler did not mean that their asthma was controlled.

Teva submitted that in relation to the briefing material instructing the representatives to 'remind the Doctor of their previous conversation ie the imminent phase out of Becotide and Becloforte', it assumed that the Panel was eluding to the service introduction contained within the representatives' folder (although this was not stated) and noted the following:

- There were approximately 1.8 million patients in the UK receiving prescriptions for CFC-containing beclometasone inhalers to control their asthma
- CFC-containing beclometasone inhalers would not be available for this patient group by around June 2008
- It was not an option 'to do nothing'. These patients would have to be changed to an alternative product.

Given this current environment the service introduction was introduced because many PCTs advocated a 'switch' of CFC-containing aerosol formulations to CFC-free formulations without patient review. This was not in the best interest of the patient and if simply switched to another product at an equivalent therapeutic dose uncontrolled patients would remain uncontrolled. The service introduction in the words of the Panel 'suggested that the phase out of Becotide and Becloforte be used as the opportunity to review all asthmatics'. The service introduction clearly advocated against switch. Teva failed to see how it could be more explicit in its materials, but it was currently reviewing them all in light of the Panel's comments.

It should be apparent that the service detail aid together with the service introduction advocated review in line with the BTS guidelines of all patients not just specific groups, unless directed to do so by the practice. The service introduction simply recognised that practices had to implement a CFC transition within the next year. The service as stated within the service detail aid in addition to reviewing all asthmatics could provide effective implementation of a CFC transition programme. The main message was to review patients before considering a change. This was a very responsible message to give to practices and was in line with the General Practitioner in Airways Group's advice given on their web-site. The transition was going to happen anyway, Teva wanted to use it as an opportunity to improve asthma care.

'The representative was instructed to tell the doctor that the service could help him: provide a full therapeutic review of all asthmatics; identify controlled asthmatics for a straight change to a CFC-free equivalent for both metered dose inhalers and breath actuated inhalers if required and identify sub-optimally controlled patients for review through a clinic.'

Teva noted the above statement whilst factually correct must be taken in context within which it was presented to practices as well as the current environment. The Panel had again eluded to the service introduction contained within section 7 of the representative training folders provided. It had already been highlighted that the service detail aid contained the main communication messages in relation to the promotion of the service.

The service introduction could be used with practices interested in implementing a CFC transition as part of the service. There were approximately 1.8 million UK patients on CFC-containing beclometasone aerosols who would have to be changed to another product within the next year. The NHS did not have the resources to provide an extra 1.8 million face to face consultations. Therefore the basis of Teva's communication was that some practices would like to identify controlled patients, defined as controlled following GP review of the 77 data fields per patient contained within the clinical assessment and submitted as part of the practice baseline assessment 'for a straight change to a CFC-free equivalent for both metered dose inhalers and breath actuated inhalers if required' and deployed the nurse advisors to review within a face to face consultation the uncontrolled patients which the practice selected following the same review. Teva stressed however that if the practice wished every patient within the practice to have a face to face consultation then it would implement that action. As stated above the service provided a full therapeutic review for all asthmatics. It appeared that the Panel had quoted one or two sentences in isolation from the whole document highlighting them out of the original context. The service introduction discouraged against 'switch', did not advocate switch, as the Panel implied. The item advocated 'reviewing asthma patients prior to the transition'.

The briefing material did not mention the BTS/SIGN guidelines.

Teva noted that the Panel incorrectly stated that the briefing material did not mention the BTS/SIGN guidelines. The BTS guidelines were mentioned in the following service materials utilised by the sales force with practices:

- The service bridging piece – brief description of the service left with the GP during a promotional call
- The service detail aid (this was presented to all practices during the non promotional call) – the BTS guidelines were mentioned on pages 2, 5 and 7
- The service introduction did not re-state the BTS/SIGN guidelines as these messages would have been made clear to the practice when the representative presented the service detail aid. There was no need for repetition. The service introduction would be used to support page 7 of the detail aid (practice benefits) when presenting the bullet point 'Can provide effective implementation of a CFC-Free transition programme.'

In addition other service materials eg the representatives' briefing document clearly stated that 'The objective of the Enhanced Asthma Care Service is to provide General Practice with a facilitation platform for the systematic identification and review of asthmatic patients in line with the BTS/SIGN guidelines'.

'Representatives were briefed to state that the result of the service was that 'CFC transition is implemented for the practice and patient care is optimised for your asthmatic patients'. The service detail aid itself stated that one of the benefits of the service was that it could provide an effective implementation of a CFC-free transition programme. This benefit was, however, listed after other benefits which referred to clinical assessment and the BTS guidelines.'

Teva submitted that as contained within the service detail aid, the service could provide an effective implementation of a CFC-free transition programme following a full clinical assessment, however 'The objective of the Enhanced Asthma Care Service is to provide General Practice with a facilitation platform for the systematic identification and review of asthmatic patients in line with the BTS/SIGN guidelines'. Teva submitted that it could not have made this any clearer in its customer facing documents or indeed representative briefing material.

'The Panel noted that with regard to patient identification, poorly controlled asthmatics were defined as those who used an agreed number of short acting bronchodilators over a 12 month period. These people would be sent a symptom questionnaire. The Panel assumed that if patients had used less than the agreed number of short acting bronchodilators over a 12 month period then they would be defined as controlled asthmatics. In this regard, however, the Panel considered that merely noting a patient's use of reliever medication was only a surrogate marker for asthma control. It was possible that some patients who did not use a lot of short acting bronchodilators were nonetheless not optimally controlled. The Panel did not consider such identification on its own constituted clinical review.'
Teva submitted that this appeared to be one of the major misunderstandings in the Panel's ruling and why it considered that the service was a 'switch service'.

An identical data set was collected as part of a full clinical assessment for all asthma patients within participating practices ie for both controlled (defined as reliever use above an agreed level over the previous 12 months) and uncontrolled patients. This comprised an additional 76 data sets (in addition to reliever use) that were collected for all patients as part of the clinical assessment and constituted the 'electronic baseline assessment'.

- Therefore the only action that was different for controlled and uncontrolled patients was that uncontrolled patients received a symptom questionnaire but controlled patients did not require one because of their low level of reliever use (defined by the practice) and no asthma symptoms in the GP notes. Teva noted that if the practice wished to send all asthma patients a symptom questionnaire then this could be stated on the authorization form and would be implemented by the agency if required.

- The 'electronic baseline assessment' was then presented to the practice. All 77 collected data sets relating to patients were then reviewed on an individual basis by the nurse and the GP in order for the GP to decide a course of action. This could clearly be seen on of the service authorization form. It should be noted that even if a patient used a low number of reliever inhalers, that patient might have other treatment issues eg admission to hospital with an asthma attack, then the practice might decide that the patient was not controlled and treat the patient accordingly. Reliever use was only used as an initial marker for asthma control. The use of reliever inhalers was a marker advocated by the BTS. In other words every patient received a full clinical review prior to the GP authorizing a specific course of action and SABA use alone was not used to agree a course of action for an individual patient.

Controlled patients were therefore treated in exactly the same way as uncontrolled patients, the same data sets were collected for both groups of patients and no action was taken for any patient without a full clinical assessment and presentation of the baseline assessment to the GP. The GP would authorize mandated actions at this point.

BTS/SIGN recognised and stated that the level of use of short-acting bronchodilators 'is a marker of poorly controlled asthma'. The use of short-acting bronchodilators (relievers) was a well recognised marker within primary care in assessing asthma control and was referenced as such on all national and international guidelines published on asthma. Teva included a synopsis of the guidelines and the affirmation of the importance of reliever usage as a marker of asthma control.

Teva submitted that putting aside the statement in the Panel's ruling that 'a patient's use of reliever medication was only a surrogate marker for asthma control' national and international guidelines suggested the contrary. Teva had evidence that other industry services used reliever use alone to define an uncontrolled patient. In relation to the comment that

reliever use alone did not constitute a clinical review Teva agreed and this was why a much broader clinical review was conducted as part of the service.

'The Panel noted that it was stated that the nurse advisors would identify all patients that satisfied the review inclusion criteria that the representatives has discussed and agreed with the lead GP in the practice. The instructions to representatives stated that the service design could focus on either patient control and symptoms or CFC transition. The advantages included 'enables practice to complete CFC transition.'

Teva submitted that the service authorization form allowed the practice to confirm exactly which patients that it wished to review. The GP performed the role of Data Controller as defined within the Data Protection Act 1998. Whether a CFC-free transition was incorporated as part of the service depended on practice choice.

'The representative's responsibilities with regard to completion of the practice mandate included confirmation of 'which ICS (inhaled corticosteroids) patients were to be reviewed – patients receiving CFC-containing or all patients.'

Teva submitted that the representative fulfilled an administrative role in relation to the service and simply asked the practice to confirm on the service authorization form which patient groups the practice would like to review. The choice of patients reviewed was the decision of the practice as it controlled the service at all times. The agency simply implemented the practice requirements.

'The Panel considered there was a discrepancy within the instructions and with regard to the selection criteria for practices to be offered the service, and queried whether the primary selection criterion really was that they must have key GPs and staff who realised the importance of identifying and reviewing asthma patients who were sub-optimally controlled and should be established on a more effective therapy.'

Teva noted that the clinical assessment completed for all asthma patients within the practice could only serve to help identify patients who needed additional review. Given that there were still 1,400 deaths due to asthma per year according to Asthma UK, which also stated that as many as 90% of the deaths were preventable - the service could help to address this situation. The Panel's statement outlined above was not helpful as it stated that it queried the primary selection criteria but did not state its findings. Teva noted that practices undertaking the service signed to state 'that the services provided are in the best medical interest of our patients and that we (GPs), retain complete control of the service at all times'. The service was in the interest of patients and benefited the NHS whilst maintaining patient care.

'The representatives training presentation detailed the representatives on-going role once the practice had signed up to the programme and they were told that this was the start not the end of their role. When scheduling the first date for [agency] staff to attend the surgery representatives were to make sure that they could be there to inter alia, remind the practice of the sponsor and 'Build the relationship three ways'. The representative was to keep in regular contact with the practice.'

Teva submitted that the representative's role was purely administrative in relation to the delivery of the service. The representative took agency staff into the practice, introduced them, and then left to carry out their normal day's activities. It was only courteous for the sponsor to introduce the agency personnel to the practice. The service was expensive and Teva was trying to build its pedigree as a market-leading respiratory house. The service would assist the practice in the pro-active management of its asthma patients. As the local nurse advisor was likely to deliver the service to other practices within that representative's geography the phrase 'building the relationship three ways' was meant to convey a spirit of partnership between the supplier and sponsor ie agency and the representative. The training slides were presented at a national conference. The representative might for example provide practical administrative advice to the nurse on 'how to find the practice, the best place to park' etc. These messages were contained within the verbal commentary covering the presentation of the slides. The representative was briefed to keep in regular contact with the practice following the service provision as permitted by the Code. When companies delivered an added-value service to a customer they wanted to ensure that the service and its implementation met with practice approval.

'No advice was given in the presentation regarding the relevant clauses of the Code and the limited non-promotional role of the representative once the practice had signed up.'

Teva submitted that representatives received ABPI training on their initial training course (details were given). Additionally all representatives were asked to read through Clause 18 of the Code and they sat the ABPI examination.

Teva submitted that it was incorrect to state that no advice was given regarding the relevant clauses of the Code. Immediately before the service presentation the sales force received a presentation in relation to the Code, including the provision of added-value services. Information on ABPI training was not initially requested by the Panel. All representatives as part of their initial training received this presentation.

It should also be noted that the service representative training document stated the requirements of the Code in relation to the provision of medical and educational goods and services.

Teva submitted that also as part of the training all representatives were required to sit the ABPI examination. This ensured that they were fully conversant with the Code and its application to medical and educational goods and services at the time of the training. The examinations were marked and the representatives de-briefed. Anyone who failed the

examination was asked to successfully complete the examination prior to discussing the service with practices.

'The Panel noted Teva's comments about some PCT's approach in switching patients form CFC to CFC-free treatment without patient review. It appeared from the materials submitted that it was possible for a practice to decide to use the Teva service for such a switch.'

Teva submitted that this was not possible. Practices signing up to the service, on the authorization form, agreed that following the patient identification a nurse review was conducted. As the miquest based extraction tool identified and conducted a clinical assessment at the same time, it was not possible to identify patients without conducting a full clinical assessment. A 'switch' was therefore technically not possible.

'Documentation in this regard was included in the Teva service e.g. the practice treatment mandate. The practice treatment mandate identified five groups of patients: Group 1 was controlled on CFC corticosteroids; Group 2 was controlled on CFC-free corticosteroids; Groups 3 and 4 were sub-optimally controlled either on CFC or CFC free corticosteroids and Group 5 were non-responders.'

Teva submitted that the service identified and produced a full clinical assessment for all patients at steps 1 to 5 of the BTS/SIGN guidelines. In addition to the treatment mandate described above the practice also confirmed a treatment protocol for all other patient groups within the service authorization form.

'A template letter, headed 'EACS Immediate Medication Change', was also provided which appeared to indicate that the patient was being switched from CFC to CFC-free without clinical review.'

Teva submitted that this was factually incorrect. Any course of action for any patient was only authorized by the GP following a full clinical assessment and the GP having reviewed the practice baseline assessment and discussed each individual patient. All letters relating to service delivery were only used after this point. There was a whole range of template service letters to cover all likely service outcomes. The practice might use the template letters provided, modify their content or indeed use their own letter providing it met with Code requirements. All template letters utilised on the service had been provided previously.

'The Panel queried why such a template letter should be provided at all if practices were chosen because they wanted to identify and review asthma patients who were sub-optimally controlled and establish them on a more effective therapy.'

Teva submitted that the immediate medication change letter was used when the practice had decided that following a full clinical assessment it wished to change patients to a different medicine without a face to face consultation. In such instances most practices informed the patient of the change by letter. The provision of template letters was purely to save the practice time in creating its own. Most practices responded positively to the provision of such a letter. There was a range of template letters used on the service.

'A number of items in the training materials referred to the service enabling practice to complete CFC transition. The Panel noted its comments above about the discrepancy between the stated aims of the service and the training and other materials.'

Teva disagreed with the Panel's comments. It had to accept that the CFC transition was high on the agenda of most practices and PCTs at present. The materials clearly communicated the practice benefits that could be achieved as a direct result of the service; these included but were not limited to a CFC transition. Indeed the service detail aid listed the practice benefits as follows:

- Proactively identify patient's current level of asthma control at each step of the BTS guidelines
- Full therapeutic review of those patients needing further review or medication change to improve their control
- Patients attending clinic would have their inhaler technique assessed to ensure that they could use their device properly
- Clinical assessment, in accordance with the BTS guidelines, including key measures to help meet GMS targets and achieve QOF points through the completion of asthma templates
- Could provide effective implementation of a CFC-free transition programme
- Identify controlled patients for potential step down in line with BTS/SIGN guidelines
- Identify patients whose treatment regime falls outside of current guidelines for review e.g. high dose steroid/long-acting beta agonist without inhaled corticosteroids
- Extra resources to assist the practice improve outcomes in asthma.

Teva submitted that the service benefits highlighted above were a fair representation of the benefits delivered to practices which might request the service.

'There were no instructions about what representatives and nurse advisors were to do if all the practice required was a switch form CFC to CFC-free treatment. This was a significant omission.'

Teva submitted that as previously stated, representatives and nurse advisors had been trained and informed that a 'switch' was not permissible under the Code. This was the message that representatives had been briefed to give to practices. If this was a 'significant omission' Teva considered it should have been clarified with Teva prior to the Panel making its ruling.

In addition Teva's service material, namely the representatives' briefing document informed the representative that 'Clause 18.4 prohibits switch services'. Hence the representative was clearly briefed not to promote the service as a 'switch' service.

'The Panel had some serious concerns about the

arrangements for the service in question and noted that switch services were expressly prohibited under the Code. In this regard the Panel specifically queried the representatives' role in discussing and agreeing inclusion criteria with the GP, the possible inclusion of patients controlled on CFC corticosteroid preparations and the provision of a template 'switch' letter.'

Teva submitted that the representative confirmed which patients the practice wished to review ie had a purely administrative role in assisting the practice to complete certain sections of the service authorization form and this activity was permissible under the Code. Teva did not provide a template 'switch' letter as previously discussed. The Panel's ruling contained many repetitions of the same point which Teva had addressed earlier.

In relation to the inclusion of patients controlled on a CFC corticosteroid the BTS advocated the review of all patients every three months in order to ensure that the patient's asthma was controlled on the lowest effective dose of their medicine. Not only was this a legitimate group of patients to review, their review could potentially result in significant savings being achieved by the NHS in relation to prescription costs.

'In the Panel's view the representatives' briefing material contained mixed messages regarding switch programmes. On one hand representatives were reminded that switch services were prohibited, on the other they were told to 'sell' the service on the basis that, inter alia, prescribers could use it to identify controlled patients and do a straight change to a CFC beclomethasone product (CFC transition appeared to be a greater priority than clinical assessment of patients); template letters for immediate medication change were provided.'

Teva submitted that representatives' training materials made it abundantly clear that 'switch' services were prohibited. Teva was reviewing all training materials in line with the ruling.

Teva noted that the Panel had changed the words from how they appeared within the service introduction. It stated 'Identify controlled patients and do a straight change to a CFC beclomethasone product'. However, the service introduction stated 'identify controlled patients (defined by you) for a straight change to a CFC free equivalent for both MDI and BAI inhalers if required'.

At no point did the service material state a CFC-free beclometasone product. This was an incorrect and invalid insertion. Teva was disappointed that these inaccuracies were not picked up by the Panel and rectified before release of the ruling. This was a fundamental flaw in the Panel's ruling as this wording could constitute grounds for a reader to believe the service was designed for 'switch' purposes. A CFC-free equivalent could mean a number of ICS molecules eg fluticasone, budesonide, mometasone, ciclesonide or indeed the change to a combination inhaler.

'The Panel considered that the material for the service should have been consistent and made it abundantly clear that switch services without clinical assessment were wholly unacceptable. There should have been no room for doubt.'

Teva submitted that the service materials conveyed the required messages in line with the Code.

'On balance the Panel considered that the representatives' briefing material was ambiguous such that it might be seen by some as advocating a course of action which was likely to lead to a breach of the Code as alleged.'

If this point was in relation to a breach of Clause 15.9 Teva was willing to accept this ruling. Teva had however endeavoured to communicate a sophisticated asthma review service in as consistent a manner as possible.

'The Panel then considered whether the circumstances were such that a formal report under paragraph 8.2 of the Constitution and Procedure should be made to the Code of Practice Appeal Board. The Panel decided not to make such a report as there was clinical review for uncontrolled patients and some element of review to establish which patients were controlled. Some of the instructions referred to the requirements of Clauses 18.1 and 18.4 and their supplementary information.'

Teva submitted that controlled patients and uncontrolled patients received the same review process ie a full clinical assessment and such an assessment was then presented to the GP in the form of a baseline assessment in order that the GP could decide an appropriate course of action for each patient. The Panel presumed (incorrectly) that reliever use only formed the clinical review for controlled patients. This was incorrect. Given that assumption Teva could see why the Panel might have ruled the service in breach of Clauses 18.1 and 18.4 as it would become a 'switch' service. This was a significant issue that needed to be addressed by the Appeal Board.

In conclusion Teva noted that the Panel as outlined above had made three major and incorrect assumptions in reaching its ruling:

- The service was a switch service
- Controlled patients did not receive a full clinical review
- A 'switch letter' was provided as part of the service.

Teva submitted that its appeal unambiguously proved, together with the service documents provided, that that these assumptions were not valid. Teva's comments together with its initial submission demonstrated that the service and materials complied fully with Clauses 18.1, 18.4 and 9.1 of the Code. Teva submitted that it was not in breach of Clause 2.

APPEAL BOARD RULING

The Appeal Board acknowledged the clinical value of a review service in asthma given the number of uncontrolled patients and the imminent discontinuation of CFC corticosteroid inhalers. Very many patients even if well controlled, would soon have

to be changed over from CFC-containing products to CFC-free alternatives.

The Appeal Board noted that practices were offered the service in question before representatives knew what their prescribing choices would be. In that regard the asthma review service was not linked to the prescription of any medicine. No breach of Clause 18.1 was ruled. The appeal on this point was successful.

The Appeal Board, however, noted that section 2B of the Practice Treatment Mandate had to be completed by the Teva representative and the GP. In such circumstances the Appeal Board considered it highly likely that, where such therapy was appropriate, the GP would feel pressurised to specify Qvar, Teva's CFC-free beclometasone. The Appeal Board considered it unacceptable for the representative to be present when the GP recorded his/her prescribing decision and in this regard upheld the Panel's ruling of a breach of Clause 18.4 of the Code. The appeal on this point was unsuccessful.

Notwithstanding its ruling of a breach of Clause 18.4 of the Code, overall the Appeal Board did not consider that high standards had not been maintained. No breach of Clause 9.1 was ruled. It thus followed that there was no breach of Clause 2 of the Code and the Appeal Board ruled accordingly. The appeal on these points was successful.

Complaint received	**3 July 2007**
Case completed	**10 December 2007**

CASE AUTH/2020/7/07 *NO BREACH OF THE CODE*

ANONYMOUS v MERCK SHARP & DOHME

Januvia cost model

A member of a primary care trust (PCT) medicines management team alleged that a computer cost model for Januvia (sitagliptin), which a Merck Sharp & Dohme representative had presented at a PCT meeting, was misleading. The model showed the potential cost impact on a PCT of prescribing Januvia.

The complainant alleged that the model made unsubstantiated claims about hospital costs for heart failure and other hospital costs. Also, the costs of competing medicines did not seem to be right. The average costs of medicines used as an alternative seemed in some cases to be overstated (sulphonylureas) and in others to be understated (glitazones). This seemed to be due to dose errors.

The Panel noted that the Januvia model entitled 'Budgetary impact of Januvia (sitagliptin) for the treatment of type 2 diabetes when patients on diet, exercise plus metformin monotherapy require additional glycaemic control' was described as a one year budget impact model designed to answer the question 'What is the financial impact of using Januvia in my local area?'. The Panel had been provided with printouts of screens of the model. It did not have the model itself.

The Panel was concerned that the first screen and the results summary screen featured the disclaimer 'Whilst MSD has made every effort to ensure that the information in the Januvia Budget Impact Model was correct at the time of its incorporation, MSD takes no responsibility for any omissions, errors or inaccuracies, whether at the time of such incorporation or subsequently. Any individual using the Januvia Budget Impact Model is ultimately responsible for the exercise of his/her own judgement as to its application to any given budget …'. The Panel noted, however, that the Januvia budget impact model was promotional material and as such had to comply with the Code at its time of issue and use. It was thus not acceptable to state that the company was not responsible for errors, omissions or inaccuracies.

The screen describing the purpose of the model referred to the results being estimates. There were three major inputs. The number of patients who might be expected to use Januvia, the daily cost compared to the other oral diabetes medicines and any cost savings from Januvia in relation to a potential reduction in the incidence of adverse events otherwise associated with other diabetes medicines (eg heart failure and hypoglycaemia) or to potential reductions in the need for self-monitoring blood glucose.

The representatives' briefing material stated that the model would answer the question 'What is the financial impact of using Januvia in my local area?' The representatives were then told of the three major inputs into the model and that the user must interpret and apply any results with caution and when discussing the disclaimer to emphasise that the model was to be used as a guide and that all results were simply estimates. The customer must feel comfortable with the accuracy of the calculation if they want to apply them. Representatives were also told that there were 'certain inherent limitations to the results from this particular model, which are attributable to this type of model being speculative in nature'. The representatives were also instructed that the health benefits of using Januvia were not specifically examined except as they impacted on costs eg reduced hypoglycaemia, self-monitoring of blood glucose and incidence of heart failure.

The Panel noted that the complainant was concerned about the costs of heart failure and other hospital costs. The annual incidence rates for heart failure were calculated from the 34.5 month pioglitazone and placebo rates in the PROactive study (Dormandy *et al*). The Panel noted that the study rate for the proportion of pioglitazone patients with at least one heart failure event needing hospital admission 149/2605 (5.72%) was reproduced in Merck Sharp & Dohme's response as the 'non in-patient' rate. It was possible that this error also occurred in the actual model as it was repeated in the cost offsets heart failure screen headed 'probability of heart failure (approximately 3 years)' which stated that 5.72% patients taking glitazones required no hospital admission and 5.07% required hospital admission vs 5.07% and 5.72% respectively in the published paper. It appeared that similar errors were made with the placebo data which was used for the sulphonylurea costs and the Januvia costs. The rates for pioglitazone patients observed by Dormandy *et al* were then applied to rosiglitazone. A footnote (g) to the heart failure section in cost offsets read 'Dormandy et al (2005) recruited high risk patients; that is patients with evidence of macrovascular disease' whereas the published paper stated that eligible study patients had to have evidence of *extensive* macrovascular disease (emphasis added). The study authors noted pioglitazone improved cardiovascular outcome in type 2 diabetics who were at high cardiovascular risk and that their results 'should also be applicable to patients who have not had a macrovascular event …' , nonetheless this was an assumption and had not been proven. Footnote (c) explained that the model assumed that Januvia had the same risk as placebo in Dormandy *et al* and footnote (h) stated 'Note: there is currently no long-term data assessing the risk of heart failure for patients on Januvia'. The assumption that Januvia had the same heart failure risk as placebo had thus been made in the absence of long-term data.

Nonetheless the Panel noted that the Januvia SPC did not refer to any cardiovascular problems associated with therapy. The Panel considered that the footnotes were not adequate warnings about the assumptions made about heart failure incidence rates.

The Panel noted that the costs of heart failure were based on the 1998/9 figures published in UK Prospective Diabetes Study (UKPDS) which estimated the immediate and long-term healthcare costs associated with severe diabetes-related complications. The expected mean hospital in-patient cost of heart failure in 1998/9 was £2,221 and the expected mean annualized non-in-patient cost for macrovascular complications was given as £315. Merck Sharp & Dohme explained that these figures were then inflated to current price levels (£2,971 and £421 respectively). The Panel queried whether it was appropriate to use the expected mean figures, rather than the estimated annual hospital in-patient costs or non-in-patient costs conditional on some costs being incurred. The expected mean reflected the fact that for any complication there was only a probability that the patient would incur a cost.

The Panel noted that the briefing document advised representatives to emphasise that the cost offsets section was optional as it was speculative. Assumptions had to be made because of limited data. Representatives were reminded that the model was based on estimates and not to try to apply precise numbers.

Overall the Panel was concerned about the methodology and assumptions made in the model. The Panel queried whether the model was sufficiently robust given its general comments above. The Panel considered that the heart failure costs were misleading and not capable of substantiation as alleged, breaches of the Code were ruled.

The Panel noted that the cost of competitor products was based on national figures and as such might not reflect local prescribing habits or local costs. The Panel queried whether costs other than those arising from heart failure, hypoglycaemic events and self-monitoring of blood glucose would impact on the cost of Januvia therapy. The Panel did not consider that given the stated purpose of the model (to answer the question 'What is the financial impact of using Januvia in my local area?') that the limitations of the model were sufficiently clear or that the results generated were only estimates. Although local population data could be used, national medicine costs were used. The Panel considered that the model was misleading in this regard and a breach of the Code was ruled.

Upon appeal by Merck Sharp & Dohme the Appeal Board noted the company's submission that only 8.5% of the cost of Januvia could be offset by a potential reduction in the incidence of adverse events associated with other oral treatments for diabetes compared with Januvia (eg heart failure with glitazones and hypoglycaemia with sulphonylureas) or a potential reduction in the need for self-monitoring of blood glucose. It was possible not to include these cost offsets in the estimation. The Appeal Board noted that the model could estimate the cost for a PCT-defined percentage of patients eligible for Januvia or default settings could be used. The Appeal Board considered that by their nature models such as the Januvia budget impact model could only give estimates but that their intended audiences ie appropriate PCT personnel, would understand such constraints.

Although the Appeal Board considered that the transposition of figures for in-patients and non-in-patients from the PROactive study was a most unfortunate error, it noted Merck Sharp & Dohme's submission for the appeal that the error made a difference of less than 0.1% of the calculated cost. In the context of the material in question, the Appeal Board considered that the error had not materially affected the outcome. Although the Appeal Board had concerns about the introductory disclaimer it considered that the limitations of the model were clear and would be understood by the intended audience.

The Appeal Board noted that the complainant was concerned about the costs of heart failure and other hospital costs. The annual incidence rates for heart failure were calculated from the 34.5 month pioglitazone and placebo rates in the PROactive study. The Appeal Board noted that compared with other studies the heart failure rate reported in the PROactive study was a conservative value and as such was not unreasonable. The Appeal Board noted that the heart failure section cited relevant assumptions as did other sections of the cost offsets section.

The Appeal Board did not consider that the heart failure costs were misleading. Within the accepted limits of a health economic model they were capable of substantiation. No breaches of the Code were ruled.

The Appeal Board noted that the calculation of the weighted costs of competitor products was based on national figures and as such might not reflect local prescribing habits. However, the Appeal Board considered that the intended audience would understand such figures and not be misled by them. No breach of the Code was ruled.

An anonymous and non-contactable member of a primary care trust (PCT) medicines management team complained about a computer cost model for Januvia (sitagliptin) produced by Merck Sharp & Dohme.

COMPLAINT

The complainant stated that a representative from Merck Sharp & Dohme had recently visited the PCT to talk about Januvia. As part of the meeting a computer cost model was presented showing the potential cost impact on a PCT.

The complainant alleged that PCTs could be misled by this model for a number of reasons. It made unsubstantiated claims about hospital costs for heart failure and other hospital costs. Also, the costs of competing medicines did not seem to be right. The average costs of medicines used as an alternative

seemed in some cases to be overstated (sulphonylureas) and in others to be understated (glitazones). This seemed to be due to dose errors.

When writing to Merck Sharp & Dohme, the Authority asked it to respond in relation to Clauses 7.2 and 7.4 of the Code

RESPONSE

Merck Sharp & Dohme stated that the Januvia budget model was examined by the Medicines and Healthcare products Regulatory Agency (MHRA) in line with standard pre-vetting procedures, and was approved by it in its current form. Whilst Merck Sharp & Dohme appreciated that approval by the MHRA did not, by itself, indicate Code compliance, it believed that it indicated that the MHRA did not consider the material misleading, as alleged.

The complainant made two primary allegations: that the model made unsubstantiated claims with respect to hospital costs for heart failure; and that the average costs of sulphonylureas and glitazones were incorrectly calculated.

Merck Sharp and Dohme submitted that the purpose of the heart failure section of the budget model was to draw attention to potential cost offsets of Januvia in preference to glitazones, attributable to a higher expected risk of heart failure developing with the latter. Heart failure was a well-recognised adverse event associated with glitazone use.

Far from being 'unsubstantiated', all steps of the heart failure cost offset calculation were illustrated in the model, in the 'Detailed Calculations' section of the 'Cost Offsets' worksheet. The process was summarised as follows.

The cost of heart failure was calculated through the use of three published data sources:

- A publication based on data from the PROactive trial. To date, this was the only published long-term study of cardiovascular outcomes/safety with glitazones. The trial which involved 5,238 type 2 diabetics, sought to estimate the effects of pioglitazone when compared with placebo (in addition to background anti-hyperglycaemic therapy) on macrovascular events, over an average observation time of 34.5 months (Dormandy *et al* 2005).

  This source provided the data on the risk of heart failure for glitazone-managed and non-glitazone-managed patients.

- The United Kingdom Prospective Diabetes Study (UKPDS) group (Clarke *et al* 2003), reported on the development of a model to estimate the immediate and long-term health care costs associated with seven diabetes-related complications in type 2 diabetics. Costs were estimated from data on 5,102 type 2 diabetics included in the UKPDS. Given the increased risks, severity and duration of cardiovascular complications in diabetic patients compared with the non-diabetic population, it was deemed essential to base the model calculations on evidence obtained from diabetic subjects. The UKPDS was widely recognised as the reference study in this area.

  Only immediate costs were incorporated into the Januvia budget impact model, and all costs were in 1998/9 values (see below for how these had been adjusted to current values).

  This source provided the costs associated with heart failure in the UK.

- The annual report, The Unit Costs of Health and Social Care, provided detailed costing information on a variety of medical and social services in the UK. The report also provided data on the annual rate of inflation in the health sector.

  This source was used to inflate the 1998/9 cost-values from Clarke *et al* to 2005/6 levels.

The method of estimating the costs associated with heart failure in the UK could be followed in the 'Detailed Calculations' section of the 'Costs Offsets' worksheet of the model.

1 As shown in the model, the estimation began by using values from table 9 of the PROactive publication. The values provided were separated by treatment group and represented:
- the reported sample sizes (in each arm of the trial);
- the number of patients with heart failure not requiring hospitalisation;
- the number of patients with heart failure requiring hospitalisation.

2 As no single trial provided information on the incidence of heart failure for all therapies considered in this model (metformin, sulphonylureas [SUs], sitagliptin and glitazones), results from the placebo arm of the PROactive trial were assumed to apply to all non-glitazone treatments, inasmuch as heart failure was not a known side-effect of any non-glitazone oral antihyperglycaemic.

   Therefore, by dividing the number of patients with each type of heart failure by the total number in the treatment arm, the 34.5 month incidence of heart failure could be estimated as follows:

	34.5 month incidence of heart failure(%)		
Therapies	**Hospitalisation**	**Non in patient**	**Total**
Glitazone	5.07	5.72	10.79
SU	3.42	4.10	7.52
Metformin+Glitazones (fixed dose combination)	5.07	5.72	10.79
Sitagliptin	3.42	4.10	7.52

3 The third step of the detailed explanation in the model adjusted the 34.5 month incidence rate of heart failure by treatment regimen to an annualised rate.

4 Clarke *et al*, estimated the cost of managing these two forms of heart failure in the UK. Whilst the article was published in 2003, values reported in the publication were in 1998/9 £ sterling.

Although more recent estimates of the costs of heart failure might exist, as the estimate provided by this paper was exclusively in diabetics, it was seen to provide the most appropriate estimate.

Clarke *et al* provided an estimated cost for a 'hospitalised' heart-failure event. Only the costs accruing in the year in which the event occurred were included in the model. The estimated cost for this event was reported as £2,221.

An estimate for the 'non-hospitalised' heart-failure event cost was taken from the paper. It was assumed that the macrovascular event cost reported was representative of the event under analysis, at £315.

As Clarke *et al* estimated cost in 1998/9 values, the costs required inflation to current price levels. This was possible through use of the Hospital and Community Health Services (HCHS) Pay and Prices Index produced by the Personal Social Services Research Unit (PSSRU). This information was presented in the first five columns of the table below. The sixth column represented the cumulative multiplier required to transform 1998/9 values into estimated 2006 values.

Year	Index (1987/8 = 100)	Prices	Pay	Pay & Prices	Cumulative multiplier from 1998/9 prices
1998/9	180.4	2.5	4.9	4.0%	1.00
1999/00	188.6	1.2	6.9	4.5%	1.05
2000/1	196.5	-0.3	7.2	4.2%	1.09
2001/2	206.5	0.1	8.3	5.1%	1.14
2002/3	213.7	1	5	3.5%	1.18
2003/4	224.8	1.5	7.3	5.2%	1.25
2004/5	232	1	4.5	3.2%	1.29
2005/6 (E)	241.3	1.9	5.6	4.0%	1.34

As illustrated in the detailed calculations section of the budget impact model, 1998/9 values must be multiplied by 1.34 (to two decimal places) to obtain estimated 2006 values.

This allowed for the calculation of estimated inflation-adjusted costs of heart failure. These values were £2,971 and £421 for heart failure requiring hospitalisation and not requiring hospitalisation, respectively.

5 By multiplying the annual incidence rates of heart failure for each treatment regimen (step 3 by the costs identified in step 4, the annual average cost of heart failure (per person) could be identified. For a glitazone-based regimen, the total cost associated with heart failure was £60.74, and £41.33 for a non-glitazone based regimen.

6 Annual per patient costs were then multiplied by the number of patients in each treatment arm, as specified in the model. Savings made available through the use of sitagliptin were then presented in the model.

In summary, the projected excess costs associated with heart failure secondary to glitazone use were fully substantiated in the cost model, using the best evidence base available.

Merck Sharp and Dohme stated that the primary alternatives to Januvia in the current UK diabetes market were sulphonylureas and glitazones; there were a number of treatment options available in each class. In addition, each product might have various dosages available and might be recommended with a range of daily dosing levels.

As common sources of cost information such as the Monthly Index of Specialities (MIMS) and the British National Formulary (BNF) only contained details of dose ranges, and the cost per pack/presentation, it was not possible to estimate an accurate 'cost per sulphonylurea treatment day' using these sources.

In order to obtain an accurate estimate, data on average dosing levels and relative sales information for all products (including generics) were incorporated into the model.

Data used in these calculations were captured at the UK level. Therefore, while all costs were representative at the national level, there might be minor discrepancies at the local level, where prescribing rules might exist through local formularies and guidelines. Nevertheless, as noted below, the method by which the national-level figures were calculated was transparent and accessible within the model itself.

The daily treatment costs associated with sulphonylureas, glitazones and fixed-dose combinations of metformin and glitazone were estimated from several sources:

- Pack cost from MIMS, January 2007; and BNF 53 (March 2007).
- IMS Disease Analyser, as interpreted by Merck Sharp & Dohme. This database provided data on the 'average' dose levels of each sulphonylurea, separated by whether it was prescribed generically or by brand. An explanation of the IMS Disease Analyser database was included in the model: 'Note: the IMS Disease Analyser (Mediplus) is a database of anonymous patient records from more than 500 GPs over 10 years. MSD subscribed to the IMS Disease Analyser database and had direct access to the terminal. This analysis was therefore the result of "desk-based research" in house.'
- IMS Dataview 6.0, as interpreted by Merck Sharp & Dohme. This database was used to capture the number of pills of all sulphonylurea and glitazone treatments sold in the entire UK for a 12-month period.

The model contained an explanation of how the daily treatment costs of therapies were estimated, as follows:

'There are multiple brands, pack sizes and prices within each of the classes of oral antidiabetic medication (glitazone, sulphonylurea, metformin). Furthermore, for each product, there is variation in the possible dose strength and number of doses. It was therefore necessary to calculate a weighted cost according to the following steps:

1 The average daily dose of sulphonylurea and metformin from IMS Disease Analyzer. Note: the average dose per day for glitazone was assumed to be one tablet.

2 Applying this average daily dose, the average daily cost per therapy, based on IMS Dataview and MIMS January 2007.

3 Applying this daily therapy cost, the average daily cost per class based on IMS Dataview

A summary example of the weighted calculation for glitazones and glitazone/melformin fixed dose combination can be viewed.'

The full explanation of the method by which the average daily sulphonylurea cost was calculated (data on file, based on IMS Dataview 6.0 and IMS Disease Analyser, as referred to above) was provided.

The reference pack also contained a step-by-step guide on how sulphonylurea costs were estimated. The cost associated with glitazone treatment was a simpler calculation and used an identical methodology. The glitazone calculation was also presented in the budget impact model.

1 The average dose of glitazone was assumed to be one tablet per day, and two tablets per day for fixed dose combinations of metformin and glitazone.

Using the IMS Disease Analyser, the average dose of each sulphonylurea was identified, as presented below:

Molecule	Product	Average daily dose (as identified through IMS Disease Analyser) (mg)
Gliclazide	Generic	150.75
	Diamicron	89.52
Glimepiride	Amaryl	2.92
	Generic	2.82
Glibenclamide	Generic	8.79
	Daonil	8.79
	Euglucon	8.79
Glipizide	Generic	10.01
	Minodiab	10.01
	Glibenese	10.01
Tolbutamide	Generic	1,221,41

Based on the presentations available in the UK, the number of tablets required to meet the daily average dose was calculated. The average cost per tablet was then estimated from each strength of pack. The number of tablets required to meet the average daily dose was then multiplied by the cost per tablet for each pack to estimate the cost per day of sulphonylurea treatment, based on treatment with that particular pack.

2 The estimated proportion of patient days for each treatment (which reflected the relative use of each at a national level) was then multiplied by the average daily cost for each pack to allow an estimate of the average daily cost of SU therapy.

The 'Drug Costs' worksheet of the budget impact model included the option to display an example of a weighted calculation of the daily cost of glitazone and fixed dose combination treatment.

As it was conservatively assumed that the daily glitazone dose was one tablet per day (two tablets per day for fixed dose combination therapy), there was no need to estimate the number of patient days in this calculation. Rather, relative sales through the number of pills sold could be simply calculated.

In conclusion, Merck Sharp & Dohme maintained that the budget impact model for Januvia was transparent, accurate, and reflected to the fullest extent possible the best available evidence base for the costs under consideration. Specifically, the heart failure incidence and costs had been sourced from the most up-to-date and relevant papers available and the costs reflected the cost of medicine actually prescribed.

PANEL RULING

The Panel noted that the Januvia model entitled 'Budgetary impact of Januvia (sitagliptin) for the treatment of type 2 diabetes when patients on diet, exercise plus metformin monotherapy require additional glycaemic control' was described as a one year budget impact model designed to answer the question 'What is the financial impact of using Januvia in my local area?'. The Panel had been provided with printouts of screens of the model. It did not have the model itself.

The Panel was concerned that the first screen featured a disclaimer which stated that 'Whilst MSD has made every effort to ensure that the information in the Januvia Budget Impact Model was correct at the time of its incorporation, MSD takes no responsibility for any omissions, errors or inaccuracies, whether at the time of such incorporation or subsequently. Any individual using the Januvia Budget Impact Model is ultimately responsible for the exercise of his/her own judgement as to its application to any given budget …'. The Panel noted, however, that the Januvia budget impact model was promotional material and as such had to comply with the Code at its time of issue and use. It was thus not acceptable to state that the company was not responsible for errors, omissions or inaccuracies. The disclaimer appeared again on the

results summary screen.

The model featured the following sections: Purpose of the model, Diabetes in the UK, Januvia Population 1 (diabetes), Population II (therapy), Drug costs, Cost offsets and Results summary.

The screen describing the purpose of the model referred halfway down to the results being estimates. There were three major inputs. The number of patients who might be expected to use Januvia, the cost per day compared to the other oral diabetes medication and any cost savings from Januvia in relation to a potential reduction in the incidence of adverse events associated with other diabetes medications compared with Januvia (eg heart failure and hypoglycaemia) or to potential reductions in the need for self-monitoring blood glucose.

The accompanying representatives' briefing material informed representatives that the model was designed to answer the question 'What is the financial impact of using Januvia in my local area?' The representatives were then told of the three major inputs into the model and that the user must interpret and apply any results with caution and when discussing the disclaimer to emphasise that the model was to be used as a guide and that all results were simply estimates. The customer must feel comfortable with the accuracy of the calculation if they want to apply them. The representatives were also told that there were 'certain inherent limitations to the results from this particular model, which are attributable to this type of model being speculative in nature'. The representatives were also instructed that the health benefits of using Januvia were not specifically examined except as they impacted on costs eg reduced hypoglycaemia, self-monitoring of blood glucose and incidence of heart failure.

The Panel noted that the complainant was concerned about the costs of heart failure and other hospital costs. The annual incidence rates for heart failure were calculated from the 34.5 month pioglitazone and placebo rates in the PROactive study (Dormandy *et al*). The Panel noted that the study rate for the proportion of pioglitazone patients with at least one heart failure event needing hospital admission 149/2605 (5.72%) was reproduced in Merck Sharp & Dohme's response as the 'non in-patient' rate. It was possible that this error also occurred in the actual model as it was repeated in the cost offsets heart failure screen headed 'probability of heart failure (approximately 3 years)' which stated that 5.72% patients taking glitazones required no hospital admission and 5.07% required hospital admission. Dormandy *et al* stated that 132/2605 patients did not need hospital admissions (5.07%) and 149/2605 needed hospitalisation (5.72%). It appeared that similar errors were made with the placebo data which was used for the sulphonylurea costs and the Januvia costs. The rates for pioglitazone patients observed by Dormandy *et al* were then applied to rosiglitazone. A footnote (g) to the heart failure section in cost offsets read 'Dormandy *et al* (2005) recruited high risk patients; that is patients with evidence of macrovascular disease'. The Panel noted that according to the published paper eligible study patients had to have evidence of extensive macrovascular disease (emphasis added). The study authors noted pioglitazone improved cardiovascular outcome in type 2 diabetics who were at high cardiovascular risk and that their results 'should also be applicable to patients who have not had a macrovascular event …' , nonetheless this was an assumption and had not been proven. The Panel noted that footnote (c) explained that the model assumed that Januvia had the same risk as placebo in Dormandy *et al* and footnote (h) stated 'Note: there is currently no long-term data assessing the risk of heart failure for patients on Januvia'. The assumption that Januvia had the same heart failure risk as placebo had thus been made in the absence of long-term data. Nonetheless the Panel noted that the Januvia SPC did not refer to any cardiovascular problems associated with therapy.

The supplementary information to Clause 7.2, 'General', stated that 'It should be borne in mind that claims in promotional material must be capable of standing alone as regards accuracy etc.' In general claims should not be qualified by the use of footnotes and the like. The Panel considered that the footnotes were not adequate warnings about the assumptions made about heart failure incidence rates.

The Panel noted that the costs of heart failure were based on the 1998/9 figures published in UKPDS which estimated the immediate and long-term healthcare costs associated with severe diabetes-related complications. The expected mean hospital in-patient cost of heart failure in 1998/9 was £2,221 and the expected mean annualized non-in-patient cost for macrovascular complications was given as £315. Merck Sharp & Dohme explained that these figures were then inflated to current price levels (£2,971 and £421 respectively). The Panel queried whether it was appropriate to use the expected mean figures, rather than the estimated annual hospital in-patient costs or non-in-patient costs conditional on some costs being incurred. The expected mean reflected the fact that for any complication there was only a probability that the patient would incur a cost.

The Panel noted that the representatives' briefing document advised representatives to emphasise that the cost offsets section was optional as it was speculative. Assumptions had to be made because of limited data. Representatives were reminded that the model was based on estimates and not to become distracted by trying to apply precise numbers.

Overall the Panel was concerned about the methodology and assumptions made in the model. The model had to comply with, *inter alia*, Clause 7 of the Code and should not be misleading; all costs should be capable of substantiation. The Panel noted that the cost offsets were described as speculative and thus were not capable of substantiation. The Panel queried whether the model was sufficiently robust given its general comments above. The Panel considered that the heart failure costs were misleading and not capable of substantiation as alleged. A breach of Clauses 7.2 and 7.4 was ruled.

The Panel noted the company's explanation of the calculation of the weighted costs of competitor products. The representatives' briefing material explained that the detail of the calculations for metformin and sulphonylureas were not included as this was more complex and very difficult to summarize. The cost of competitor products was based on national figures and as such might not reflect local prescribing habits. The Panel noted that such costs would not necessarily reflect the actual costs in any locality. The Panel queried whether costs other than those arising from heart failure, hypoglycaemic events and self-monitoring of blood glucose would impact on the cost of Januvia therapy.

The Panel did not consider that given the stated purpose of the model (to answer the question 'What is the financial impact of using Januvia in my local area?') that the limitations of the model were sufficiently clear or that the results generated were only estimates. Although local population data could be used, medicine costs were based on national figures. The Panel considered that the model was misleading in this regard and a breach of Clause 7.2 was ruled.

APPEAL BY MERCK SHARP & DOHME

Merck Sharp & Dohme submitted that the model in question was, for various reasons, withdrawn from use as from 7 December, and would not be recommissioned in its original form. However, the Panel's ruling's in this case contained important and far-reaching implications for the use of any similar cost model by the pharmaceutical industry. As such, Merck Sharp & Dohme thought it appropriate to seek clarification on the conclusions of the Panel at appeal.

Merck Sharp & Dohme stated that the model was submitted to the MHRA as part of the normal vetting procedures for new medicines, and was approved by it. Whilst Merck Sharp & Dohme appreciated that this did not exempt it from its habitual obligations under the Code, the company noted that the MHRA made no amendments to the model as submitted for pre-vetting.

Merck Sharp & Dohme stated that the purpose of the model was simple: to demonstrate, within the accepted levels of tolerance for any health economic assessment, that the use of Januvia, in a reasonable projected proportion of those type 2 diabetics for whom it was indicated, would be expected to have a minimal budgetary impact, when compared with the costs of alternative treatments. The model was used by Merck Sharp & Dohme healthcare managers (not representatives) in their ongoing discussions with appropriate PCT personnel.

Merck Sharp & Dohme submitted that the base case analysis in the model was for a nationally representative population of 100,000 people. For this population, the net cost of Januvia treatment was estimated as, on average, a little under £4,300 per annum – a relatively small and insignificant proportion of overall PCT budgets. By far the greatest contributory factor to this assessment was medicine acquisition costs. A very small contribution (8.5%) was composed of cost offsets resulting from three ancillary benefits of using Januvia: a lower expected incidence of heart failure compared with glitazones; a lower expected incidence of hypoglycaemia compared with sulphonylureas and, as a result of the low risk of hypoglycaemia, a possible reduction in the need for expensive self-monitoring of blood glucose.

Merck Sharp & Dohme noted that the complainant's apparent primary concern about the model, and the great majority of the points considered by the Panel in making its ruling, did not relate to the calculation of medicine acquisition costs per se, but rather the cost offset calculations, especially that concerning the expected rate of heart failure with glitazones. While the latter calculations must, of course, stand on their own merits, Merck Sharp & Dohme noted that, even if all the cost offsets were removed from the calculation (which the model allowed the user to do), the primary conclusion of the model – that Januvia was effectively cost-neutral in terms of PCT budgetary impact – remained unchanged, with an increase in net cost of approximately £399.

Merck Sharp & Dohme submitted that the Panel's ruling of breaches of Clause 7.2 and 7.4 was not made on any single overriding factor, but on a variety of different issues, as addressed below:

Disclaimer statement

Merck Sharp & Dohme noted that the Panel's concern over the wording of this statement. Its original intent was to take account of the difficulties inherent in any health economic analysis with respect to pricing differences or inconsistencies, changing circumstances, assumptions, extrapolations, etc, and to draw the user's attention to the fact that any results or conclusions deriving from the model were, by their nature, estimates, based on the reference data cited in the model. It was certainly not intended to be a carte blanche for the inclusion of inaccurate or misleading statements or data.

For the purposes of clarity, the wording for such disclaimers in future health economic models and documents had been redrafted as follows:

'Merck Sharp & Dohme Limited ("MSD") acknowledges that this [describe in detail] health economic model (the "Model") has been created for the purpose of promoting [add product name].

Whilst the health economic data included in this Model have been checked for accuracy, this Model is intended to be indicative, not predictive, of budget impact. There are certain assumptions, caveats and extrapolations built into the methodology of this Model, some of which are dependent upon input from you (the "User")

The User should note that any results and/or conclusions deriving from this Model are, by their nature, estimates only'.

That said, Merck Sharp & Dohme submitted that, by its very nature, the original disclaimer statement could not represent a breach of the Code, as it did not contain any data or conclusions which, in themselves, could be deemed to be misleading or inaccurate.

'In-patient' versus 'non-in-patient' heart failure incidence

Merck Sharp & Dohme noted that the Panel had correctly identified an inadvertent error in the figures attributed to these two incidence rates, which were accidentally transposed ('in-patient' figures being labelled as 'non-in-patient', and vice versa). Factual errors of this nature were always regrettable, and Merck Sharp & Dohme was grateful to the Panel for noting it. Nevertheless, the error needed to be viewed in the context of the overall effect it had on the conclusions of the model. In fact, it made a difference of approximately £4 out of a total of £4,297 (0.093%). By any standards, unfortunate though the error might have been, it had a negligible impact on the conclusions drawn from the model, and could not reasonably be considered to be misleading in any accepted sense of that term, particularly when viewed in the overall context of a health economic model.

Use of the PROactive study as a benchmark for the assessment of heart failure incidence with glitazone therapy

Merck Sharp & Dohme noted the Panel's apparent concerned that the PROactive study (involving pioglitazone) was not a fair benchmark for the assessment of heart failure rates with glitazone use in the general population.

Merck Sharp & Dohme took advice on the appropriate benchmark trial to use in this assessment. The universal recommendation was that PROactive was the best reference available. This trial was the only long-term glitazone trial focusing specifically on cardiovascular outcomes. Furthermore, the heart failure data arising from it were particularly robust, inasmuch as all cases reported during the trial were subsequently subject to post-hoc independent scrutiny and adjudication by third-party experts.

Merck Sharp & Dohme submitted that it was true that, as a secondary outcome study, PROactive recruited patients with pre-existing macrovascular disease. However, a crucial point was that these pre-existing conditions were ischaemic in nature. The Panel's citation of the study authors' remarks on the effects of pioglitazone on cardiovascular outcome in patients with or without a history of macrovascular events again confused ischaemic events (the events the authors were referring to) and heart failure. Ischaemic heart disease (IHD) and heart failure might, of course, co-exist, but they were quite separate pathological entities. Patients with a history of, or known predisposition to, heart failure would have been excluded from the trial, on account of the well-recognised association between glitazone use and exacerbation or instigation of heart failure, a fact that had been recognized, since launch in the labelling for both pioglitazone and rosiglitazone. In addition, as noted by the Panel, the fact that the PROactive trial included patients with macrovascular disease was noted in the list of assumptions and particular notes appended to the relevant section of the model (see below).

Merck Sharp & Dohme submitted that similar heart failure rates to that observed in PROactive had been seen in other long-term glitazone trials (eg ADOPT, with rosiglitazone) and – with both agents – in a recent meta-analysis (Nesto *et al* 2007). The use of PROactive as the benchmark study was justified and reasonable. The results of PROactive were completely in line with the general body of evidence on this subject and the nature of the study was signalled quite clearly to the user in the appended notes.

Extension of pioglitazone results to rosiglitazone

Merck Sharp & Dohme submitted that the Panel commented in passing that the results from PROactive with pioglitazone had been extended in the model to rosiglitazone as well, implying that this was not a valid extrapolation. On the contrary, as mentioned above, heart failure was a well-recognised side-effect of glitazone use, irrespective of which of the two currently marketed compounds was involved. This was evidenced by the broadly similar heart failure rates between the two agents seen in a recently published meta-analysis examining this issue (Nesto *et al*.). The extension of rates seen with pioglitazone to rosiglitazone use was concordant with available data, and not misleading.

Absence of long-term heart failure data with Januvia

Merck Sharp & Dohme noted that the Panel had noted that the assumption that Januvia would have the same heart failure risk as placebo in the PROactive study had been made in the absence of any long-term data (although, again, it recognised that this fact was stated in the list of assumptions and notes).

While it was true that the maximum trial duration for a published Januvia study was currently 52 weeks, there was a very large difference between the expectation of a heart failure event in glitazone-treated as opposed to Januvia treated patients. The known increased incidence of heart failure with glitazone use was associated with a quite specific and well-recognised pathophysiological precipitating event observed with glitazone agents, namely an increase in fluid volume. As well as leading to peripheral oedema and haemodilution, this increased fluid volume placed an additional load on the myocardium, resulting, in susceptible patients, in an increased risk of developing overt heart failure.

Merck Sharp & Dohme reiterated, as noted by the Panel, the Januvia SPC did not refer to any cardiovascular problems related to therapy. As such, Merck Sharp & Dohme submitted that the assumptions in the model were warranted and not misleading.

The use of 'footnotes'

Merck Sharp & Dohme noted that the Panel had commented on the use of 'footnotes' in the calculation of heart failure incidence rates, citing the supplementary information to Clause 7.2 of the Code. Some of these notes had been referred to above.

Merck Sharp & Dohme queried whether these notes should be considered as footnotes in the generally accepted sense. They were in quite large type, and were not cited at the foot of the page in question, being appended to the cost calculation table to which they referred. As such, Merck Sharp & Dohme submitted that they were addenda and additional information relating to the specific data table, rather than footnotes as such.

Merck Sharp & Dohme submitted that leaving matters of definition aside, the Panel's view raised serious issues concerning the use of any health economic model; and highlighted the very significant differences between such models and the more familiar area of interpreting clinical trials results. In the latter case, the results or findings were usually fairly clear-cut, and Merck Sharp & Dohme fully accepted that inappropriate interpretation or use of such results was not mitigated by the addition of footnotes. Health economics, however, was not an exact science. Any health economic model was built upon a foundation of assumptions and approximations, often more or less speculative in nature. Without such assumptions and approximations, it would be impossible to generate any model whatsoever. Within broad limits, no one set of assumptions was the correct one, although of course some might accord more with common sense and scientific opinion than others. It was thus of crucial importance that the assumptions on which the model was based were completely transparent, so that the user could properly assess the appropriateness of the conclusions to his or her individual circumstances. This was the purpose of the notes appended to the table in question.

Merck Sharp & Dohme noted that the Panel questioned the use of words like 'speculative' to describe the methodology and data used in the model, taking that to mean that the conclusions derived from it were incapable of being robustly substantiated, and thus in breach of the Code. Again, Merck Sharp & Dohme suggested that practically no health economic model was totally substantiable in the strict sense. By necessity, the cost model approach involved ambiguities and uncertainties. The most that could be done was to provide the user with adequate information on which to draw their own judgement as to the relevance of the information provided. The issues around whether the particular assumptions etc in the present model were reasonable ones was addressed elsewhere but Merck Sharp & Dohme submitted that the underlying principle of making these assumptions plain was both sound and necessary.

Heart failure cost calculation

Merck Sharp & Dohme noted that the Panel had queried whether it was appropriate to use the mean expected cost of heart failure (from UKPDS 65), as opposed to the estimated annual cost, conditional on some costs being incurred. Merck Sharp & Dohme submitted that given that PROactive presented the data for in-patient and non-in-patient episodes of heart failure, this might be an understandable viewpoint. However, as the original article was based on a study conducted in the UK, reflecting appropriate treatment and classification patterns, it was decided to base the costs on the final expected (or unconditional) data reported by the authors.

Furthermore, Merck Sharp & Dohme submitted that as the value suggested for in-patient care by the Panel was actually higher than that used in the model, a greater cost offset through the use of Januvia would have been estimated had the Panel's suggestion been implemented; although the cost of non-in-patient care was lower, once values were inflated to current levels using generally accepted criteria (£5,654 and £155, respectively), the total cost offsets increased by around £160. This adjustment represented a change of less than 4% in the overall outcome, and its omission represents a conservative approach to the estimation of cost offsets available through the use of Januvia. Indeed, all assumptions used in the model tended towards the more conservative interpretation of the available data.

Possible hidden costs

Merck Sharp & Dohme noted that the Panel had queried whether costs other than those arising from heart failure, hypoglycaemic events and self-monitoring of blood glucose would impact on the cost of Januvia therapy. Merck Sharp & Dohme took this to mean that the Panel was concerned that there might be other ancillary costs associated with the use of Januvia, and/or other agents assessed, that were not taken account of in the model. Merck Sharp & Dohme submitted that it was not aware of any such additional potential costs. The adverse reactions associated with Januvia use, as detailed in the SPC, were generally non-specific and non-severe, and would not be expected to have any significant impact on the overall cost impact of the product.

Local costs versus national data

Merck Sharp & Dohme noted that the Panel was concerned that, although the stated purpose of the model was to answer the question 'What is the impact of using Januvia in my local area?', the medicine costs involved were based on national figures. The Panel considered this to be so misleading that an additional breach of Clause 7.2 was ruled.

This was a particularly harsh ruling. Self-evidently, members of PCT management teams – at whom this model was directed – would be interested in the impact of Januvia on local budgets, hence the question above. Equally self-evidently, it would be wholly impractical, if not impossible, to produce separate sets of figures for every individual PCT. Nor was it conceivable that acquisition costs within any one PCT

would differ so markedly from average national costs as to render the overall conclusion of the model invalid. It was common practice to estimate the average cost of treatments through the use of data on national prescribing trends, as conducted in this model. A similar methodology was utilised by the Scottish Medicines Consortium.

Merck Sharp & Dohme again emphasised that the purpose of the model was to provide users with a broad assessment of the sort of costs that might be expected to be associated with the use of Januvia in their locality. It was not intended to supply a detailed and accurate local costing correct to the nearest penny; nor would it be expected to do so. In the disclaimer statement, in the briefing document, and at various points within the model itself, it was made quite clear that the costs involved were approximations, and that the data in the model should be interpreted at a local level in accordance with local practice and circumstances. Particular limitations and assumptions inherent in the model were duly noted in addenda to data tables, etc. The fact that the Panel found these statements also to be in breach of the Code evidently raised a significant concern.

Merck Sharp & Dohme submitted that the above dealt with all of the substantive points raised by the Panel in its ruling. To summarise, with the exception of a minor factual error which had a negligible effect on the conclusions drawn from the model, the assumptions and data on which the model was based were reasonable; the limitations and essentially approximate nature of the calculations were clearly signalled at multiple points and overall, the conclusion of the model that use of Januvia in the specified population would not lead to significant increases in local prescribing budgets was fair and warranted.

In all of these respects, Merck Sharp & Dohme maintained its view that the model was not misleading and therefore it appealed the rulings of breaches of Clauses 7.2 and 7.4.

APPEAL BOARD RULING

The Appeal Board noted that the Januvia budget impact model was a one year model designed to answer the question 'What is the financial impact of using Januvia in my local area?' The Appeal Board was provided with printouts of screens of the model. It did not have the model itself.

The Appeal Board noted from Merck Sharp & Dohme's submission that only 8.5% of the cost of Januvia could be offset by a potential reduction in the incidence of adverse events associated with other oral treatments for diabetes compared with Januvia (eg heart failure with glitazones and hypoglycaemia with sulphonylureas) or a potential reduction in the need for self-monitoring of blood glucose. It was possible not to include these cost offsets in the estimation. The Appeal Board noted that the model could estimate the cost for a PCT-defined percentage of patients eligible for Januvia or default settings could be used. The Appeal Board considered that by their nature models such as the Januvia budget impact model could only give estimates but that their intended audiences ie appropriate PCT personnel, would understand such constraints.

The Appeal Board noted that in the model the study rate for heart failure incidence in-patient figures from the PROactive study had been transposed with non-in-patient figures. Although it considered that this was a most unfortunate error, the Appeal Board noted Merck Sharp & Dohme's submission for the appeal that it made a difference of less than 0.1% of the calculated cost. In the context of the material in question, the Appeal Board considered that the error had not materially affected the outcome. Although the Appeal Board had concerns about the introductory disclaimer it considered that the limitations of the model were clear and would be understood by the intended audience.

The Appeal Board noted that the complainant was concerned about the costs of heart failure and other hospital costs. The annual incidence rates for heart failure were calculated from the 34.5 month pioglitazone and placebo rates in the PROactive study. The Appeal Board noted that compared with other studies the heart failure rate reported in the PROactive study was a conservative value and as such was not unreasonable. The Appeal Board noted that the heart failure section cited relevant assumptions as did other sections of the cost offsets section.

The Appeal Board did not consider that the heart failure costs were misleading. Within the accepted limits of a health economic model they were capable of substantiation. No breach of Clauses 7.2 and 7.4 were ruled. The appeal on this point was successful.

The Appeal Board noted that the calculation of the weighted costs of competitor products was based on national figures and as such might not reflect local prescribing habits. However, the Appeal Board considered that the intended audience would understand such figures and not be misled by them. No breach of Clause 7.2 was ruled. The appeal on this point was successful.

Complaint received **16 July 2007**

Case completed **11 January 2008**

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During its consideration of this case, the Panel sought advice from Professor Martin Buxton BA (Soc Sci), Professor of Health Economics and Director of the Health Economics Research Group at Brunel University, and independent health economics consultant, who provided an opinion in a personal capacity.

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CASE AUTH/2026/7/07

CONSULTANT IN ELDERLY/STROKE MEDICINE v BOEHRINGER INGELHEIM

Actilyse press release

A consultant in elderly/stroke medicine alleged that an Actilyse (alteplase) press release, issued by Boehringer Ingelheim, contained inaccurate and misleading claims about safety, outcomes and mortality to the extent that it appeared that alteplase saved lives as mortality was reduced from 17.3% to 11.3%. Such an effectiveness claim and the Department of Health's choice to indicate that thrombolysis reduced death and disability made it appear that alteplase was a life-saving treatment whereas in fact it saved autonomy as trial evidence showed no significant life-saving potential. Furthermore and worse was that Boehringer Ingelheim failed to publicly disclose additional information presented to the National Institute for Health and Clinical Excellence (NICE) ie that in the UK the mortality with alteplase was 20.6% vs 17.3% quoted in its press release. The UK press was misled and misinformed and the evidence was there in the detail but not in plain view on the NICE website to disprove such false promotional claims about the effects of Actilyse. Was Boehringer Ingelheim working to high standards and keeping the industry in a state of good repute and increasing the confidence in the industry to tell the truth about its products in a fair and balanced manner?

The Panel noted that the press release was issued by the UK company's German corporate colleagues and placed on its corporate website. It was an established principle under the Code that UK companies were responsible for the acts/omissions of their overseas affiliates that came within the scope of the Code.

The press release was headed 'Actilyse (alteplase) recommended by [NICE] for treatment of acute ischaemic stroke. NICE Appraisal Committee concludes that alteplase is clinically and cost effective'. Text beneath read 'For medical media, outside the US only'. The press release referred to the UK publication of the appraisal. A quotation from the company read '… we hope that this recommendation from NICE will allow more patients with qualifying stroke in the UK to benefit from treatment with Actilyse'. The penultimate paragraph of the 'Notes to Editor' on the final page of the press release read 'Please be advised. This release is from the Corporate Headquarters of Boehringer Ingelheim and is intended for all international markets. This being the case, please be aware that there may be some differences between countries regarding specific medical information including licensed uses. Please take account of this when referring to the material'. The Panel noted that the UK company had not referred UK doctors or media to the site. The Panel did not know whether the German company had done so. The Panel noted the comments in the press release about the intended audience. Nonetheless the Panel noted that the press release referred to a UK public document and discussed benefit to UK patients. The Panel noted that Boehringer Ingelheim twice referred to it as a press release relating to UK matters and explained that procedures had been put in place to ensure that such releases complied with the Code. The Panel considered that given its content, the press release was subject to the UK Code.

Actilyse was indicated *inter alia* for fibrinolytic treatment of acute ischaemic stroke. The summary of product characteristics (SPC) stated that such treatment must be started within 3 hours of the onset of stroke symptoms and after prior exclusion of intracranial haemorrhage by means of appropriate imaging techniques.

According to the press release NICE had recommended the use of alteplase for the treatment of patients with acute ischaemic stroke. The press release referred to data in the NICE report which, based on a series of trials, demonstrated efficacy for treating acute ischaemic stroke within 3 hours and showed that 'alteplase resulted in significantly better outcomes for patients in terms of death and dependency at 3 months compared with placebo'.

The press release also explained that the NICE appraisal committee had noted independent European data which assessed the safety and efficacy of alteplase in routine clinical practice and showed that mortality rates following alteplase treatment were 'even lower in routine clinical practice than had previously been seen in randomised clinical trials (11.3 percent vs 17.3 percent)'. More information about the data source appeared in the 'Notes to Editor' section.

Section 5.1 of the Actilyse SPC, Pharmacodynamic properties, Acute stroke, referred to two studies where a significantly higher proportion of patients had a good outcome (no/minimal disability) compared with placebo, results which were not confirmed in 3 other studies wherein the majority of patients were not treated within 3 hours of stroke onset. However an analysis of all patients in these studies treated within 3 hours of stroke onset confirmed the beneficial effect of alteplase. The risk difference vs placebo for a good recovery was 14.9% despite an increased risk of severe and fatal intracranial haemorrhage. The data did not allow a

definite conclusion to be drawn on treatment effect on death. Nevertheless overall the benefit/risk of alteplase, given within 3 hours of stroke onset and taking into account the SPC's precautions was considered favourable.

The Panel noted that it was clear from the outset that the press release related to alteplase and treatment of acute ischaemic stroke. It was acceptable to discuss the benefit which might flow from using a medicine for its licensed indication so long as such discussion was placed clearly in the context of the licensed indication and otherwise complied with the Code.

The press release did not state that mortality was reduced from 17.3% to 11.3% as alleged by the complainant. Rather these figures were presented as a comparison of mortality rates seen in routine clinical practice vs randomised clinical trials. The press release made this clear. No breach of the Code was thus ruled on this point.

The Panel noted that the press release discussed mortality data. The Panel noted the SPC statement that the data did not allow a definite conclusion to be drawn on the treatment effect on death. The press release implied that the data in this regard was unequivocal and that was not so in relation to treatment of acute ischaemic stroke. The press release was misleading in this regard and could not be substantiated. Breaches of the Code were ruled.

The Panel considered that given its rulings above high standards had not been maintained regarding the mortality data mentioned in the press release. A breach of the Code was ruled. On balance the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such.

A consultant in elderly/stroke medicine complained about an Actilyse (alteplase) press release issued by Boehringer Ingelheim Limited.

COMPLAINT

The complainant submitted that, in correspondence, Boehringer Ingelheim had stated that it would remove a press release from its website. The complainant alleged that the press release contained inaccurate and misleading claims about safety, outcomes and mortality to the extent that it appeared that alteplase saved lives as mortality was reduced from 17.3% to 11.3%. Such an effectiveness claim and the Department of Health's choice to indicate that thrombolysis reduced death and disability made it appear that alteplase was a life-saving treatment whereas in fact it saved autonomy as trial evidence showed no significant life-saving potential. Furthermore and worse was that Boehringer Ingelheim failed to publicly disclose the additional information presented to the National Institute for Health and Clinical Excellence (NICE) ie that in the UK the mortality with alteplase was 20.6% (UK specific data from the SITS-MOST (Safe Implementation of Thrombolytis in Stroke – MOnitoring STudy) data) and not 17.3% as quoted in the press release. The UK press was misled and misinformed and the evidence was there in the detail but not in plain view on the NICE website to disprove such false promotional claims about the effects of Actilyse. Was Boehringer Ingelheim working to high standards and keeping the industry in a state of good repute and increasing the confidence in the industry to tell the truth about its products in a fair and balanced manner?

When writing to Boehringer Ingelheim, the Authority asked it to respond in relation to Clauses 7.2, 7.4 and 9.1 of the Code in addition to Clause 2 alluded to by the complainant.

RESPONSE

Boehringer Ingelheim explained that NICE had reviewed the data on Actiyse for the treatment of ischaemic stroke and had posted a Final Appraisal Determination on its website on 4 May 2007; appeals had to be submitted in writing by 21 May 2007 but none were received.

A press release was placed on the Boehringer Ingelheim corporate website on 14 May 2007 by the UK company's German colleagues. This press release was stimulated by the appearance of a positive article in Scrip announcing a positive NICE appraisal for the use of Actilyse in acute ischaemic stroke and a statement on the NICE website. Confusion was caused by the terminology 'Final Appraisal Determination' which the corporate colleagues incorrectly interpreted as meaning final approval. As soon as Boehringer Ingelheim in the UK knew of the press release (16 May) it immediately asked Corporate Communications to remove it from the corporate website. This was done within 2 hours.

Boehringer Ingelheim acknowledged that, although the content of the press release was accurate, it should not have been posted on the corporate website in advance of the release by NICE of the finally approved single technology appraisal (STA) document. To clarify processes for publication of corporate press releases on UK matters a high level meeting was held in the UK between UK and corporate. In future any press release relating to UK matters originating from corporate colleagues would first be reviewed by the UK to ensure that it conformed to the Code.

The press release was reinstated unchanged by the corporate colleagues on the corporate website only after the final STA document had appeared on the NICE website in June 2007. It had since been removed from the corporate website after the submission of the present complaint to the Authority.

In response to a request for further information, Boehringer Ingelheim stated that the press release needed to be put in context since it was prepared for a global audience by German colleagues and never appeared on the UK website. UK doctors/media were never informed of or directed to the press release by Boehringer Ingelheim UK.

The content of the press release was based upon the

Final Appraisal Determination (published on the NICE website) and the Lancet publication of the SITS-MOST database. Data in the press release were given in a factual and scientific way and were direct transcripts from both these documents. The SITS-MOST was a prospective, open, multicentre, multinational, observational monitoring study for clinical centres practising thrombolysis for acute ischaemic stroke within the member states of the EU. Actilyse was licensed by the European Medicines Evaluation Agency (EMEA) in 2003 with the proviso that the SITS-MOST database was undertaken to monitor the safety and efficacy of alteplase in acute ischaemic stroke during routine clinical practice. SITS-MOST was independently run but funded by an unrestricted grant from Boehringer Ingelheim. Boehringer Ingelheim UK had no access to the SITS-MOST database or to the UK specific SITS-MOST data. The SITS-MOST database only included patients treated within the licensed indication (ie within 3 hours).

The press release stated that 'SITS-MOST recruited 6483 patients across 14 European countries and showed that mortality rates following Actilyse treatment were even lower in routine practice than had previously been seen in randomized controlled trials (11.3% v 17.3%). The incidence of symptomatic haemorrhages and functional independence at three months were comparable to those seen in randomized trials'. This was a statement of fact. In the Lancet SITS-MOST publication it was specifically stated in the findings section of the abstract '… the mortality rate at 3 months in SITS-MOST was 11.3% (701/6218: 10.5-12.1) compared with 17.3% (83/479: 14.1-21.1) in the pooled randomized clinical trials'. The reader was able to make his/her own interpretation of this statement. From a statistical point of view the confidence intervals demonstrated that the mortality data seen in the SITS-MOST database was potentially a more accurate reflection of the mortality rate that would be expected in these patients. The press release did not claim that Actilyse was a life-saving treatment.

Prior to releasing the Final Appraisal Determination NICE considered all the available evidence from the different stakeholders which included UK specific data. In Boehringer Ingelheim's view it was therefore erroneous to single out the UK-specific SITS register data over and above the other data appraised by NICE.

Additionally, with regard to the intended worldwide audience, Boehringer Ingelheim noted that under the section 'Please be advised', the press release stated that 'This release is from the corporate headquarters of Boehringer Ingelheim and is intended for all international markets. This being the case, please be aware that there may be some differences between countries regarding specific medical information including licensed uses. Please take account of this when referring to the material'. It was not intended for the UK alone.

Boehringer Ingelheim also considered that the above allegation was misleading since it did not acknowledge that the SITS-MOST data and the Final Appraisal Determination only looked at patients treated within 3 hours post stroke whereas the UK SITS data included all patients thrombolysed within and after 3 hours. Therefore the data sets were not comparable and this might account for the variations seen.

The company noted that the complainant did not refer to the point made to explain the figure of a 20.6% mortality in the UK SITS register 'Outcomes reflect the higher NIHSS (stroke severity score) of UK patients and poorer outcomes usually seen in this country but are otherwise consistent with the excellent safety profile elsewhere in Europe'. It was well known that the prognosis for patients undergoing thrombolysis for acute ischaemic stroke was much improved if the stroke was of reduced severity at onset.

PANEL RULING

The Panel noted that the press release was issued by the UK company's German corporate colleagues and placed on its corporate website. It was an established principle under the Code that UK companies were responsible for the acts/omissions of their overseas affiliates that came within the scope of the Code.

The Panel noted that the press release, dated 14 May 2007, was headed 'Actilyse (alteplase) recommended by National Institute for Health and Clinical Excellence for treatment of acute ischaemic stroke. NICE Appraisal Committee concludes that alteplase is clinically and cost effective'. Text beneath read 'For medical media, outside the US only'. The press release referred to the UK publication of the appraisal. A quotation from a senior company spokesman read '… we hope that this recommendation from NICE will allow more patients with qualifying stroke in the UK to benefit from treatment with Actilyse'. The penultimate paragraph of the 'Notes to Editor' on the final page of the press release read 'Please be advised. This release is from the Corporate Headquarters of Boehringer Ingelheim and is intended for all international markets. This being the case, please be aware that there may be some differences between countries regarding specific medical information including licensed uses. Please take account of this when referring to the material'. The Panel noted that the UK company had not referred UK doctors or media to the site. The Panel did not know whether the German company had done so. The Panel noted the comments in the press release about the intended audience. Nonetheless the Panel noted that the press release referred to a UK public document and discussed benefit to UK patients. The Panel noted that Boehringer Ingelheim twice referred to it as a press release relating to UK matters and explained that procedures had been put in place to ensure that such releases complied with the Code. The Panel considered that given its content, the press release was subject to the UK Code.

The Panel considered that the press release implied that the final NICE report had been issued and that was not so. The Panel noted that although Boehringer Ingelheim had acknowledged a breach on this point it did not consider that the complainant had made an allegation on this point and thus made no ruling on this matter.

The Panel noted that Actilyse was indicated *inter alia* for fibrinolytic treatment of acute ischaemic stroke. The summary of product characteristics (SPC) stated that such treatment must be started within 3 hours of the onset of stroke symptoms and after prior exclusion of intracranial haemorrhage by means of appropriate imaging techniques.

The Panel noted that according to the press release NICE had recommended the use of alteplase for the treatment of patients with acute ischaemic stroke. The press release referred to data in the NICE report which, based on a series of trials, demonstrated efficacy for treating acute ischaemic stroke within 3 hours and showed that 'alteplase resulted in significantly better outcomes for patients in terms of death and dependency at 3 months compared with placebo'.

The press release also explained that the NICE appraisal committee had noted the SITS-MOST data which assessed the safety and efficacy of alteplase in routine clinical practice and showed that mortality rates following alteplase treatment were 'even lower in routine clinical practice than had previously been seen in randomised clinical trials (11.3 percent vs 17.3 percent)'. More information about the SITS- MOST data appeared in the 'Notes to Editor' section.

Section 5.1 of the Actilyse SPC, Pharmacodynamic properties, Acute stroke, referred to two studies where a significantly higher proportion of patients had a good outcome (no/minimal disability) compared with placebo, results which were not confirmed in 3 other studies wherein the majority of patients were not treated within 3 hours of stroke onset. However an analysis of all patients in these studies treated within 3 hours after stroke onset confirmed the beneficial effect of alteplase. The risk difference versus placebo for a good recovery was 14.9% despite an increased risk of severe and fatal intracranial haemorrhage. The data did not allow a definite conclusion to be drawn on treatment effect on death. Nevertheless overall the benefit/risk of alteplase, given within 3 hours of stroke onset and taking into account the SPC's precautions was considered favourable.

The Panel noted that it was clear from the outset that the press release related to alteplase and treatment of acute ischaemic stroke. The Panel noted that it was acceptable to discuss the benefit which might flow from using a medicine for its licensed indication so long as such discussion was placed clearly in the context of the licensed indication and otherwise complied with the Code.

The Panel noted that the press release when discussing SITS-MOST data did not state that mortality was reduced from 17.3% to 11.3% as alleged by the complainant. Rather these figures were presented as a comparison of mortality rates seen in routine clinical practice vs randomised clinical trials. The press release made this clear. No breach of Clause 7.2 was thus ruled on this point.

The Panel noted that the press release discussed mortality data. The Panel noted the SPC statement that the data did not allow a definite conclusion to be drawn on the treatment effect on death. The press release implied that the data in this regard was unequivocal and that was not so in relation to treatment of acute ischaemic stroke. The press release was misleading in this regard and could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

The Panel considered that given its rulings above high standards had not been maintained regarding the mortality data mentioned in the press release. A breach of Clause 9.1 was ruled. On balance the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such.

Complaint received 24 July 2007

Case completed 31 October 2007

CASE AUTH/2028/7/07

NOVO NORDISK v SANOFI-AVENTIS

Promotion of Lantus

Novo Nordisk complained about claims for 24-hour glycaemic control in the promotion of Lantus (insulin glargine) by Sanofi-Aventis. Novo Nordisk alleged that claiming 24-hour control without stating that duration of glycaemic control (duration of action) was dose dependent was not accurate information based on and reflecting an up-to-date evaluation of all available evidence and it misled health professionals.

Novo Nordisk noted that the only reference cited by Sanofi-Aventis was from an isoglycaemic 24-hour clamp study (Lepore *et al*, 2000), in which the average duration of action was substantially shorter than 24 hours (20.5±3.7), at a Lantus dose of 0.35units/kg. Sanofi-Aventis had emphasised that in 16 out of the 20 patients, the average duration of action would have been longer, but the clamp investigation was stopped at 24 hours according to the trial protocol. Had the study lasted longer the average duration of action would have been close to or over 24 hours. However Novo Nordisk was concerned about the 4 patients (20%) in which the average duration of action was much shorter than 24 hours.

Klein *et al* (2007) compared the duration of action of Lantus in type 2 diabetes, using a euglycaemic clamp technique and concluded that the duration of action was dose-dependent.

Novo Nordisk alleged that the findings of these studies highlighted the need to modify the 24-hour claim of Lantus to provide accurate information to health professionals.

Novo Nordisk further noted that the Lantus summary of product characteristics (SPC) did not state that it conferred 24-hour glycaemic control and only stated that 'Lantus contains insulin glargine, an insulin analogue, with prolonged duration of action'. Furthermore the SPC correctly noted that 'The time course of action of insulin and insulin analogues such as insulin glargine may vary considerably in different individuals or within the same individual.' Therefore Novo Nordisk alleged that to claim a 24-hour duration of action for Lantus, without stating that the action was dose-dependent, contradicted the SPC.

Finally, since the launch of Lantus, accumulating clinical experience had shown that a significant proportion of type 1 diabetics required twice daily dosing (Garg *et al*, 2004, Albright *et al*, 2004).

On the basis of the above Novo Nordisk alleged that the claim of 24-hour control was exaggerated, misleading and not capable of substantiation.

The Panel noted that on a poster and a leavepiece the claim '24 hour glycaemic control' appeared as a strapline beneath the Lantus product logo. 'Once daily 24-hour glycaemic control' appeared in a similar position on another poster. On a leaflet and leavepiece 'Once Daily 24-Hour' appeared as part of the product logo. In a patient booklet there were a number of references to Lantus working for 24 hours.

The Panel noted that Sanofi-Aventis had submitted three papers in support of the claim – Lepore *et al*, Porcellati *et al* (2007a) and Porcellati *et al* (2007b). Lepore *et al* had studied the pharmacokinetic and pharmacodynamic effects of Lantus in 20 patients using an isoglycaemic 24-hour clamp technique. The authors reported that Lantus had a peakless, nearly 24-hour duration of action. The mean duration of action was 20.5±3.7 hours. However, the authors observed that the duration of action noted for Lantus was probably an underestimate and it was likely that in 16/20 patients it would have been longer than 24 hours. In order to determine this with accuracy, the study would have had to have been conducted over a longer period of time but this would have been unacceptable to patients. The authors further noted that the dose of Lantus was well within the range used in type 1 diabetics. It was also noted that as patients were only studied once with Lantus, there was no opportunity to examine intrasubject variability.

Porcellati *et al* (2007a) presented results on 24 patients with type 1 diabetes treated with Lantus once daily for two weeks. After 14 days of treatment all subjects underwent an euglycaemic clamp for 24 hours. The results showed that Lantus maintained glycaemic control in all patients for at least 24 hours.

Porcellati *et al* (2007b) compared the pharmacokinetics and pharmacodynamics of Lantus after a first injection and then again after one week of once daily use. The results showed that after one week of use Lantus had an earlier onset and longer duration of action compared with the first day of its use. The authors commented that the duration of action was underestimated because in some subjects end of action was beyond the 32 hour time limit of the study. The authors further noted that intrasubject variability of Lantus was lower after one week of use.

The SPC stated that Lantus was an insulin analogue with a prolonged duration of action. It should be administered once daily at any time but at the same time each day. The dosage and timing should be individually adjusted. Section 5.1 included a graph comparing the activity profile in patients with type 1

diabetes of insulin glargine and NPH insulin. The graph showed that the activity profile of insulin glargine was similar between 15 and 24 hours (which was when the observation period ended).

The European Public Assessment Report (EPAR) stated that the median time-action profile in type 1 diabetes indicated that Lantus displayed a moderate sustained glucose lowering activity over 24 hours compared to a distinct peak in activity with NPH insulin.

It appeared that the data in the SPC and EPAR was the Lepore data.

The Panel was concerned about the strength of the evidence prior to the Porcellati *et al* data, when the materials were approved and issued. However it considered that taking into account all the data supplied by Sanofi Aventis there was data to support the claim for 24 hour glycaemic control. The Panel considered that the SPC did not appear to allow twice daily dosing. The Panel did not consider that the failure to state that glycaemic control was dose dependent meant that the claim for 24 hour control was inaccurate, misleading or inconsistent with the SPC as alleged. In the Panel's view health professionals would be well aware that dose was an important consideration.

The Panel considered that the claim for 24 hour glycaemic control was capable of substantiation and was not exaggerated or misleading as alleged. It was not inconsistent with the SPC. No breach of the Code was ruled in relation to each of the items at issue. The Panel did not consider that Sanofi-Aventis had failed to maintain high standards. All of these rulings were appealed by Novo Nordisk.

The Appeal Board noted that on one poster and the leavepiece the claim '24 hour glycaemic control' appeared as a strapline beneath the Lantus product logo. 'Once daily 24-hour glycaemic control' appeared in a similar position on the other poster. On the leaflet 'Once Daily 24-Hour' appeared as part of the product logo. The patient booklet had a number of references to Lantus working for 24 hours.

The Appeal Board noted that of the data provided in substantiation of the claims at issue, the only data available when the complaint was made was Lepore *et al* which examined duration of action of Levemir, not its efficacy in terms of glycaemic control.

In the Appeal Board's view, in the context of diabetes, 'control' referred to glycaemic control ie the maintenance of blood glucose between set parameters. The Appeal Board noted that Lantus was a basal insulin designed to provide a background, constant suppression of blood glucose. Section 5.1 of the SPC included a graph comparing the activity profile in patients with type 1 diabetes of insulin glargine and NPH insulin. The graph showed that the activity profile of insulin glargine was smooth, peakless and almost constant between 9 and 24 hours (which was when the observation period ended).

The Appeal Board noted that no type 1 diabetic would be controlled solely on Lantus and only about half of type 2 diabetics would be controlled on a combination of Lantus and oral agents. Most diabetics would thus require short-acting insulin, in addition to Lantus, to cope with daily glucose peaks resulting from meals. The Appeal Board thus considered that a once daily dosage or a 24-hour course of action for a basal insulin did not equate to 24-hour glycaemic control.

The Appeal Board considered that claims for 24-hour control or 24-hour glycaemic control were not capable of substantiation and were exaggerated and misleading in that regard. The Appeal Board ruled breaches of the Code. The Appeal Board did not consider that Sanofi-Aventis had failed to maintain high standards.

Novo Nordisk also complained about a book authored by Joseph JM Fraser, published by Wiley, 'Joe's Rough Guide to Diabetes' book. Although Sanofi-Aventis' logo was on the back of the book there was no statement regarding the extent of the company's involvement and a breach of the Code was alleged.

Novo Nordisk also alleged that a chart in the book contained information regarding the onset of action, the peak of action and duration of action of some insulin preparations which was not consistent with the relevant SPCs.

Sanofi-Aventis stated in one of its replies during the inter-company discussion, that its only involvement has been to purchase copies to provide health professionals (as an educational service, not as a promotional item) and considered it as a valuable resource with considerable educational value for this audience. In this case, it would further increase the need for providing accurate, fair and balanced information. This book clearly failed to provide such basic information.

Novo Nordisk was very concerned that Sanofi-Aventis considered the content was fair and accurate and of significant educational merit when the book clearly tried to highlight differences between Lantus and Levemir that were direct market competitors. Novo Nordisk thus alleged that the book was clearly in breach of the Code and requested that Sanofi-Aventis withdrew it from distribution. Indeed, Novo Nordisk queried whether the dissemination of such misleading information under the guise of an educational aide warranted the issue of a corrective statement to the recipients of this book relating to the claims/'facts' contained therein.

The Panel noted that the back cover of the book included the Sanofi-Aventis logo and a statement 'Because health matters'. Sanofi-Aventis had no role in the initiation, creation or production of the book. The copies that it purchased cost less than the maximum £6 plus VAT permitted for promotional aids. The book was aimed at teenagers with diabetes; the foreword suggested that the book ought to be

available to every young diabetic and to anybody involved in helping young people to grow up with diabetes.

The Panel considered that the purpose of the book was not entirely clear. Sanofi-Aventis' written submission stated that it was provided to health professionals to increase their understanding of teenage life with regard to diabetes care ie as an educational resource for the health professional. The representatives' briefing material stated that it was a mixture of practical advice and personal experience; a great read for anyone but was particularly relevant to adolescents and young adults. The book was part of the support the company wanted to offer to adolescent patients. It was to be used in centres dealing with high numbers of adolescents and young people. The Panel thus considered that representatives had been instructed to use the book as a gift intended for use by patients.

The Panel noted that Clause 9.10 required that material relating to the medicines sponsored by a company must clearly indicate that it had been sponsored by that company. Sanofi-Aventis had purchased copies (at £1.25 per copy) to supply to health professionals.

The Panel did not know whether the book would have existed if Sanofi-Aventis had not purchased 20,000 copies to distribute as gifts. The Panel was concerned that the logo appeared on the book without a clear explanation as to Sanofi-Aventis' involvement. The Panel considered that on the information before it as Sanofi-Aventis had not contributed to the expenses of producing the book, it had not sponsored it and no breach of the Code was ruled in that regard.

The Panel noted Novo Nordisk's concerns about the information given about a number of insulins and the advice to discuss matters with the diabetes team. There was a direct comparison of Levemir and Lantus. The Levemir SPC stated that it was a long acting insulin analogue used as a basal insulin and that when Levemir was used as part of basal-bolus insulin regimen it should be administered once or twice daily depending on patient's needs. The duration of action was up to 24 hours. The book stated that the duration of action of Levemir was '6 to 23 hours' which was not accurate. The Panel queried whether the book met the requirements of the Code. Novo Nordisk had only cited certain clauses of the Code.

The Panel did not consider that, on the information before it, the book was unacceptable either as a promotional aid for health professionals or as a gift for use by patients. The book was well within the cost limitation for promotional aids and relevant and thus no breach was ruled.

The Panel noted Sanofi Aventis' submission that the book had been approved as required by the Code and thus ruled no breach was ruled.

Novo Nordisk Limited complained about the promotion of Lantus (insulin glargine) by Sanofi-Aventis. Novo Nordisk marketed a number of insulin products including Levemir (insulin detemir). Both Lantus and Levemir were long-acting insulins.

1 Claim that insulin glargine provided 24-hour glycaemic control

This claim appeared in the following items for health professionals: a poster (LAN 05/215 superseded in March 2007 by LAN 07/1038), a leaflet (CLI 06/023) and a leavepiece (API 06/063). The claim also appeared in a Lantus patient booklet (LAN 05/023).

COMPLAINT

Novo Nordisk alleged that claiming 24-hour control without stating that duration of glycaemic control (duration of action) provided by any insulin preparation including Lantus was always dose dependent was not accurate information based on and reflecting an up-to-date evaluation of all available evidence and it misled health professionals.

Novo Nordisk noted that the only reference cited by Sanofi-Aventis to substantiate its claim was from an isoglycaemic 24-hour clamp study (Lepore *et al*, 2000), in which the average duration of action was 20.5±3.7 hours, at a Lantus dose of 0.35units/kg, which was substantially shorter than 24 hours. During inter-company dialogue, Sanofi-Aventis had emphasised that in 16 out of 20 patients who participated in the study, the average duration of action would have been longer, but the clamp investigation was stopped at 24 hours according to the trial protocol. Sanofi-Aventis argued that in the case of continuing the clamp investigation over 24 hours the average duration of action would have been close to or over 24 hours. However Novo Nordisk had major concerns regarding the 4 out of 20 patients (20%) in which the average duration of action was much shorter than 24 hours.

Klein *et al* (2007) compared the duration of action of Lantus and Levemir in type 2 diabetes, using a euglycaemic clamp technique and concluded that the duration of action was dose-dependent in both cases.

Novo Nordisk alleged that the findings of these studies highlighted the need to modify the 24-hour claim of Lantus to provide accurate information to health professionals.

Novo Nordisk further noted that the Lantus summary of product characteristics (SPC) did not state that it conferred 24-hour glycaemic control and only stated that 'Lantus contains insulin glargine, an insulin analogue, with prolonged duration of action'. Furthermore the SPC correctly pointed out that 'The time course of action of insulin and insulin analogues such as insulin glargine may vary considerably in different individuals or within the same individual.' Therefore Novo Nordisk alleged that to claim a 24-hour duration of action for Lantus, without stating that the action was dose-dependent, contradicted the SPC.

Finally, since the launch of Lantus, accumulating clinical experience in type 1 diabetes had shown that a significant proportion of patients required twice daily dosing (Garg *et al*, 2004, Albright *et al*, 2004).

On the basis of the above Novo Nordisk alleged that the claim of 24-hour control was exaggerated and misled health professionals in breach of Clauses 7.2, 7.4 and 9.1 of the Code. As the claim was not capable of substantiation, Novo Nordisk had asked Sanofi-Aventis withdraw all materials containing this claim.

RESPONSE

Sanofi-Aventis submitted that the claim was based on the results of a pharmacokinetic and pharmacodynamic study performed to support the registration of Lantus (Lepore *et al*). Lepore *et al* measured the long-acting properties of a subcutaneous injection of Lantus using a euglycaemic clamp method for up to 24 hours. This was the gold-standard method for defining the pharmacodynamic properties of insulin. The dose of Lantus used was 0.3 units/kg body weight, which at 21 units for a 70kg person represented a dose lower than that used on average in clinical practice (typically 28-35 units). Lepore *et al* reported that in subjects receiving a single dose of Lantus, the mean glucose concentration at 24 hours (141±5mg/dl) remained below the threshold defined as demonstrating glycaemic control (150mg/dl), this being the most appropriate and scientifically valid measure of prolonged efficacy after a single insulin administration. In addition, the glucose infusion rate remained nearly constant between 3 and 24 hours after the injection.

Sanofi-Aventis submitted that Lepore *et al* provided evidence that Lantus maintained 24 hour glycaemic control when used at a normal, or even lower than normal, clinical dose, and as this was the most appropriate methodology, it was difficult to argue that results obtained by other methods rendered these results invalid. The authors discussed the fact that the mean duration of the study period was terminated at 24 hours, this was to be expected. More relevant was the fact that 16 of the 20 patients still demonstrated maintenance of glycaemic control at the final 24 hour time point.

Sanofi-Aventis submitted that two more recent papers supported the findings of Lepore *et al*. Porcellati *et al* (2007a) reported on 24 diabetic patients in a randomised, single-dose, double-blind, two-way, cross-over study, using the euglycaemic glucose clamp technique. Using a dose of 0.35units/kg body weight, which equated to approximately 24.5 units per day in a 70kg adult and therefore lower than average daily practice, all 24 Lantus patients had a satisfactory maintenance of glycaemic control at the end of the 24 hour clamp study. Porcellati *et al* (2007b) assessed Lantus using a dose of 0.3units/kg body weight in 20 diabetic patients, by clamp technique for 32 hours, and concluded that after one week of once daily dosing the median duration of action was 24 hours. This paper also noted that 24 hours was an underestimate, as in some patients the duration of end of action was beyond the 32-hour end-point of the study.
The evidence was further supported by the European Medicines Evaluation Agency (EMEA) scientific discussion (2005) which reflected the initial scientific discussion for the approval of Lantus and stated 'The median time-action profile after subcutaneous injection of insulin glargine in subjects with type 1 diabetes mellitus also indicated that insulin glargine displays a moderate sustained glucose lowering activity over 24 hours, compared to a distinct peak in activity with NPH insulin'.

In summary Sanofi-Aventis submitted that the above provided robust evidence to substantiate the claim that Lantus provided '24-hour glycaemic control'.

Sanofi-Aventis noted that Novo Nordisk suggested that the duration of action of Lantus was dose-dependent (as suggested by Klein *et al*) but failed to show that this duration was shorter than 24 hours. Sanofi-Aventis submitted that this reference described an increasing duration of action for Lantus, which was used at higher doses than in the study above. However, this paper was limited by its methodology, in which the only measure of duration was the maintenance of glucose infusion rate in the clamp methodology, not the preservation of normal blood glucose levels referred to by Lepore *et al* and Porcellati *et al*. As discussed in Klein *et al*, glucose infusion rate was not an effective measure of duration of action – it was better suited to assessing the short-term response to a meal than the ability to maintain blood glucose levels for up to 24 hours.

This deficiency in the methodology therefore limited the ability to define the actual duration of action of the insulins studied in Klein *et al*, and this was recognized by the authors. However, they acknowledged that Lantus was suited to once daily administration supporting the fact that 24-hour efficacy was likely to have been demonstrated.

Sanofi-Aventis concluded that although the duration of action of Lantus in Klein *et al* was dose-dependent, the methodology used was not appropriate to measure this, and this did not support the complainant's arguments. Although the duration of action of Lantus was dose-dependent, this would not be inconsistent with the 24-hour duration of action as an increase in the dose might simply reflect efficacy beyond this time point (as evidenced by 100% of patients having normal blood glucose levels at 24 hours with the highest dose of Lantus).

Sanofi-Aventis submitted that the evidence outlined above showed that:

- Lantus had demonstrated 24-hour efficacy through preservation of normal blood glucose levels up to 24 hours;
- an increase in dose might result in an increased effect above this, although the methodology presented was inadequate to make this assessment accurately;
- the current claim of 24-hour efficacy was consistent with the current Lantus SPC and this was not inconsistent with the duration being dose-

dependent (24-hour control had been demonstrated with a low-normal clinical dose, a higher dose would be more likely to result in an extension beyond this time-point).

PANEL RULING

The Panel noted that on the poster (LAN 07/1038) and the leavepiece the claim '24 hour glycaemic control' appeared as a strapline beneath the Lantus product logo. 'Once daily 24-hour glycaemic control' appeared in a similar position on poster LAN05/215. On the leaflet and leavepiece 'Once Daily 24-Hour' appeared as part of the product logo. In the patient booklet there were a number of references to Lantus working for 24 hours.

The Panel noted that Sanofi-Aventis had submitted three papers in support of the claim – Lepore *et al*, Porcellati *et al* (2007a) and Porcellati *et al* (2007b). Lepore *et al* had studied the pharmacokinetic and pharmacodynamic effects of Lantus in 20 patients using an isoglycaemic 24-hour clamp technique. The authors reported that Lantus had a peakless, nearly 24-hour duration of action. The mean duration of action was 20.5±3.7 hours. In their discussion, however, the authors observed that given the way in which end of action was defined, the duration of action noted for Lantus was probably an underestimate and it was likely that in 16/20 patients it would have been longer than 24 hours. In order to determine this with accuracy, the study would have had to have been conducted over a longer period of time but this would have been unacceptable to patients. The authors further noted that the dose of Lantus was well within the range used in type 1 diabetics. It was also noted that as patients were only studied once with Lantus, there was no opportunity to examine intrasubject variability.

Porcellati *et al* (2007a) presented results on 24 patients with type 1 diabetes treated with Lantus once daily for two weeks. After 14 days of treatment all subjects underwent an euglycaemic clamp for 24 hours. The results showed that Lantus maintained glycaemic control in all patients for at least 24 hours.

Porcellati *et al* (2007b) compared the pharmacokinetics and pharmacodynamics of Lantus after a first injection and then again after one week of once daily use. The results showed that after one week of use Lantus had an earlier onset and longer duration of action compared with the first day of its use. On day one the mean duration of action was 20.2 hours (17-25) vs 24 hours (22-28.5) on day seven. The authors commented that the duration of action was underestimated because in some subjects end of action was beyond the 32 hour time limit of the study. The authors further noted that intrasubject variability of Lantus was lower after one week of use.

The Lantus SPC (2006) stated that Lantus was an insulin analogue with a prolonged duration of action. It should be administered once daily at any time but at the same time each day. The dosage and timing should be individually adjusted. Section 5.1 included a graph comparing the activity profile in patients with type 1 diabetes of insulin glargine and NPH insulin. The graph showed that the activity profile of insulin glargine was similar between 15 and 24 hours (which was when the observation period ended).

The European Public Assessment Report (EPAR) stated that the median time-action profile in type 1 diabetes indicated that Lantus displayed a moderate sustained glucose lowering activity over 24 hours compared to a distinct peak in activity with NPH insulin.

It appeared that the data in the SPC and EPAR was the Lepore data.

The Panel had some concerns about the strength of the evidence prior to the Porcellati *et al* data, when the materials were approved and issued. However it considered that taking into account all the data supplied by Sanofi Aventis there was data to support the claim for 24 hour glycaemic control. The Panel considered that the SPC did not appear to allow twice daily dosing. The Panel did not consider that the failure to state that glycaemic control was dose dependent meant that the claim for 24 hour control was inaccurate, misleading or inconsistent with the SPC as alleged. In the Panel's view health professionals would be well aware that dose was an important consideration.

The Panel considered that the claim for 24 hour glycaemic control was capable of substantiation and was not exaggerated or misleading as alleged. It was not inconsistent with the SPC. No breach of Clauses 7.2 and 7.4 was ruled in relation to each of the items at issue. The Panel did not consider that Sanofi-Aventis had failed to maintain high standards and no breach of Clause 9.1 was ruled. All of these rulings were appealed by Novo Nordisk.

APPEAL BY NOVO NORDISK

Novo Nordisk stated that the major problem with Sanofi-Aventis' argument was that the evidence was based on the average duration of action of the given dose of Lantus from pharmacokinetic/dynamic clamp studies. However in real clinical practice health professionals had also to deal with patients whose basal requirement was not infrequently less than average. On the basis of Lepore *et al* the proportion of these patients with type 1 diabetes was significant at 20%. Of course, in these patients Lantus could theoretically cover a 24-hour period, but this would require a higher basal insulin dose than they really needed which could result in more hypoglycaemic events. Novo Nordisk also disagreed with Sanofi-Aventis' submission that the typical type 1 specific basal insulin dose used in clinical practice was between 28-34 units/day. Novo Nordisk produced a table of data which it submitted were exclusively from Sanofi-Aventis' trials in type 1 diabetes.

Novo Nordisk observed that in nine out of twelve trials the average dose of Lantus was below 25.5 units/day. Therefore Sanofi-Aventis' claim that the given dose in the Lepore *et al* was lower than the clinical dose typically used with Lantus was not valid.

The 0.3 units/kg/day dose for the basal insulin in type 1 diabetes was rather more typical. This meant that, if the Lepore *et al* results were extrapolated to real life, Lantus might not be suitable for once-daily dosing in 20% of patients with type 1 diabetes.

Novo Nordisk agreed that health professionals would be well aware that the dose was an important consideration, but only in case of specialists who were experienced in insulin treatment. However, this assumption was not valid. GPs were increasingly providing diabetes care for insulin-treated patients, in line with government strategy. Indeed NHS strategy in the UK envisaged diabetes being managed, for the most part, in primary care, (including more complicated insulin treatment regimens). Therefore, in this particular context, there was significant potential for 'all embracing' claims to result in patient harm. There needed to be no scope for ambiguity in claims relating to insulin products.

Novo Nordisk noted that one might argue that in case of type 1 diabetes, the majority of patients still received and probably would receive diabetes care from specialists. However the problem of the dose-dependent duration of action was equally important in type 2 diabetes as well. Considering the results from the clinical trials Sanofi-Aventis conducted in type 2 diabetes where Lantus was initiated in combination with oral hypoglycaemic agents, they reported 8-point mean blood glucose profile in 4 out of 11 trials. Novo Nordisk reproduced six graphs from Janka *et al*, (2005), Fritsche *et al*, (2003), Yki-Yärvinen *et al*, (2000) and Yki-Yärvinen *et al*, (2006) showing the difference in blood glucose profiles as measured eight times through the day ie before and after each meal, at bedtime and in the early hours of the morning, according to different insulin regimens.

Novo Nordisk alleged that the results showed that Lantus failed to maintain an adequate level of glycaemic control as measured before dinner, whilst maintaining control of pre-breakfast glucose levels. This meant a peak effect around morning hours and a significantly shorter duration of action than 24 hours at the given dose. Undoubtedly this finding might not only be exclusively indicative of the pharmacodynamic properties of the insulin preparation. However from a clinical perspective it was at least as important as the results of a complicated clamp trial. Since the promotional materials provided by Sanofi-Aventis to help GPs with insulin initiation in type 2 diabetes focussed solely on a titration based on the pre-breakfast blood glucose levels, the overall 24-hour claim indicated that there was no need to check pre-dinner blood glucose values. The misinterpretation of this claim might result in failing to attain blood glucose levels before dinner, which clearly detracted from achieving HbA1c targets in these patients.

Novo Nordisk was disappointed that the Panel only considered the results from clamp trials and omitted relevant clinical findings accumulated in both types of diabetes since the launch of Lantus. Health professionals needed to individualise insulin treatment according to blood glucose levels measured in real life, as shown by the titration and intensification of insulin therapy to target measured blood glucose levels, in the recently published '4-T' trial (Treating To Target in Type 2 diabetes) (Holman *et al*, 2007). Therefore the conflicting clinical findings should be considered when this promotional claim was evaluated.

Novo Nordisk submitted that making a valid and more precise claim of 'up to 24-hour duration' instead of '24-hour duration', would more accurately reflect the properties of Lantus.

Novo Nordisk also noted guidelines provided by the Medicines and Healthcare products Regulatory Agency (MHRA) on 24 hour claims – 'data must show clinical effect over the 24 hour period. The product should be for once daily dosing but a once daily dosing interval alone is insufficient to support a 24 hour claim' (emphasis added) (MHRA Blue Guide section 5.6). From the evidence presented above, data to demonstrate a 24 hour clinical effect was lacking, particularly from the 8 point daily glucose profiles. The MHRA update in relation to this issue stated 'Claims for fast or 24 hour relief may only be included on labelling where the claim is supported by the SPC' (MHRA Mail No. 141 Jan/Feb 2004). The Lantus SPC stated that it was suitable for once daily doing, and stated nothing to support a 24 hour claim.

On the basis of the evidence presented above, Novo Nordisk alleged that the '24 hour' claim for Lantus was in breach of Clauses 7.2, 7.4 and 9.1.

COMMENTS FROM SANOFI-AVENTIS

Sanofi-Aventis submitted that Novo Nordisk's appeal appeared to comprise several components, each of which would be addressed individually:

- That the 24 hour duration that had been demonstrated was based on an average value and that as some patients might have a less than average response, it was wrong to make this claim.
- An assumption that primary care physicians were not as knowledgeable as secondary care diabetologists.
- A collection of data from patients with type 2 diabetes demonstrating that there could be a statistically significant increase in blood glucose concentration between pre-breakfast and pre-dinner readings in patients receiving Lantus.

The 24 hour duration was an 'average' value

Novo Nordisk argued that although a 24 hour duration had been demonstrated, this was based on an average value and suggested that in a normal clinical setting some patients would have a response below average. Sanofi-Aventis submitted that in general terms, this would be expected of any medicine in any therapy area and it was unrealistic to accept such an argument as justification that a claim be invalid (else almost all efficacy claims for any product would be negated).

Sanofi-Aventis submitted that more specifically, the argument proposed with reference to the table of data

submitted by Novo Nordisk was that the range of Lantus doses in the trials included in the table was in some instances less than the typical 28-35 units for a 70kg man. The reader was asked to consider that this range of doses reflected real life practice and to assume that as some of these studies demonstrated an average dose lower than 28 units, and conclude that the duration of action would be less than the 24 hours already demonstrated. Sanofi-Aventis submitted that, as with the complaint, no evidence was proposed that demonstrated that, at the Lantus dose used in these studies, a duration of action less than 24 hours had been demonstrated.

Although Novo Nordisk argued that in clinical practice patients might receive less than 28 units of Lantus, this did not imply that the duration of action would fall below 24 hours. The data provided in response to the complaint demonstrated that Lantus had a 24 hour duration of action even at the lowest dose used, 0.30 units/kg, equating to 21 units for a 70kg person and 15 units for a person of 50kg (Porcellati, *et al*). In the table of studies provided by Novo Nordisk, the average dose of Lantus (weighted by study size) was just over 28 units, more than 33% above the 21 unit dose at which 24 hour action had been confirmed. In total, 11 out of 13 studies reported doses in excess of 21 units. (Of the two that fell below, one was a short phase II study with only three weeks allowed for dose titration, a situation not reflective of clinical practice where periods of up to three months to reach an optimal dose were not unusual). Finally, this observation was made before any account was taken of the fact that over 52% of patients in these trials were female, and assuming that each weighed approximately 50kg, a lower dose of insulin would be expected to have been required (28-35 units in a 70kg person equated to 20-25 units in a person of 50kg).

In summary, Sanofi-Aventis submitted that although Novo Nordisk had suggested that real life practice might result in daily doses of Lantus below the 28-35 dose range typical for a 70kg man, it had not provided any evidence that, at such a lower dose, the duration of action of the product would be below the 24 hours claimed in the materials. On the contrary, a 24 hour period of action had been demonstrated at doses of as low as 0.3 units per kg – 21 units for a 70kg man, 15 units for a 50kg woman.

Assumption on primary care physicians' level of knowledge

Sanofi-Aventis agreed with the Panel's view that health professionals would be aware of considerations relating to dose and would not be misled by this claim of 24 hour efficacy (which was in itself robust). A suggestion that there was a lack of knowledge amongst the primary care sector was discourteous to clinical colleagues, especially given that diabetes was an increasingly common disease and comprised a significant component of general practice workload (eg comprising over 15% of the General Medical Services clinical contract points).

Experience in type 2 diabetes

Sanofi-Aventis noted that Novo Nordisk had submitted eight-point blood glucose profiles for four studies in type 2 diabetes. How these graphs were meant to be interpreted was unclear, although the text indicated that it was to expect a low blood glucose in the morning and an increase in the evening, indicating that the latter was as a result of decreased efficacy as the end of a 24 hour dosing period of Lantus was reached, suggesting a duration of action of less than this. This interpretation of the results might be credible if the studies were performed with a dose of Lantus given only in the evening – an increase in blood glucose before the following evening's dose would indeed reflect worsening control as the 24 hour time period was reached. However, the studies presented were mixed with respect to the time of day that Lantus was given – both morning and evening dosing was represented:

- In Janka *et al* (2005), all patients received Lantus in the morning. This study demonstrated very effectively that when Lantus was given first thing in the morning 24 hour control was apparent, with the 3am blood glucose level (longest interval after dosing) remaining as low as that measured at the start of the day.

- In Fritzche *et al* (2003), there were two groups, one received Lantus in the morning and one received Lantus in the evening. This study demonstrated that over a 24 hour time period, the blood glucose profiles for patients receiving Lantus in the morning or in the evening were almost superimposable, suggesting that any variation was not related to the duration of effect of Lantus but due to the effect of eating during the daytime, which resulted in a peak in blood sugar levels with each meal (which then declined post-meal due in part to the action of Lantus).

- In Yki-Yärvinen *et al* (2000) and Yki-Yärvinen *et al* (2006), patients received Lantus in the evening. Although not acknowledged in the appeal, these studies demonstrated that Lantus was effective in improving the entire 8 point blood glucose profile across 24 hours compared to baseline levels, and the authors concluded that Lantus demonstrated a peak-less and prolonged duration of action and that its use was justified in the treatment of type 2 diabetes.

Sanofi-Aventis submitted that despite the fact that patients in these studies received Lantus in either the morning or the evening, exactly the same pattern emerged in each instance. The lowest blood glucose level was apparent overnight/early in the morning as a result of the prolonged overnight fast, and as daytime passed and meals were taken, blood glucose levels rose to a peak immediately after eating and then declined subsequent to each meal. This was the normal physiological pattern (Riddle *et al*, 2006) and, as would be expected, this pattern was constant and not related to the time of day at which Lantus was given, indicating that this effect was not linked to the duration of the product. In summary, these studies did not support the notion that Lantus had a duration of action of less than 24 hours. Janka *et al* clearly

demonstrated excellent 24 hour control. Finally, these observations were consistent with Heise and Pieber (2007) that summarised that, in type 2 diabetes, the duration of action of Lantus was in excess of 24 hours.

Conclusion

In summary, Sanofi-Aventis submitted that the evidence presented with the complaint firmly demonstrated that Lantus maintained glycaemic control for up to 24 hours at doses as low as 0.30 units/kg (21 units for a 70kg subject, 15 units for a 50kg subject). Novo Nordisk had not presented any data that led to a different conclusion and had in fact confirmed that in normal clinical practice the vast majority of patients with type 1 diabetes would require treatment with at least this dose and on average 33% more. In type 2 diabetes, Novo Nordisk had demonstrated that there was a normal fluctuation in daytime glucose levels as a result of peaks related to eating, and that rather than this reflecting a decrease in the efficacy of Lantus as a 24 hour period was reached, this pattern was constant regardless of treatment with Lantus being given at the start or end of the day.

Sanofi-Aventis submitted that the claim for 24 hour efficacy for Lantus was substantiable, not misleading and not inconsistent with the SPC and that complied with both the letter and the spirit of the Code and all applicable regulations.

COMMENTS FROM NOVO NORDISK

Novo Nordisk highlighted some of the difficulties surrounding the definition of 'duration of action' in clamp trials. Duration of action of the investigated insulin preparation was usually defined in two ways:

- the time from trial medicine administration until a smooth glucose infusion rate profile was consistently below 0.5mg/kg/min (Klein *et al*, 2006) and/or
- the period between onset of action (detailed definition could be found in Lepore *et al*) and end of action (defined as a time at which plasma glucose consistently increased to >150mg/dl).

Novo Nordisk alleged that both definitions used arbitrary cut-off points which were predefined by the investigators. There was no official guide or consensus with regard to the definition of pharmacokinetic parameters in clamp studies. More importantly there was no guidance on how to interpret the results from these studies for clinical practice. In clamp studies any deterioration from the pre-defined clamped blood glucose level (5.5mmol/l or 7.2mmol/l in case of euglycaemic or isoglycaemic clamp trials respectively) was a clear sign of the waning pharmacodynamic effect of the investigated insulin preparation. Assuming the argument was accepted that the first definition (rather than the methodology as pointed out by Sanofi-Aventis) had some limitations, mainly due to the difficulty in interpretating the results for clinical practice, Novo Nordisk focused on the second definition which was accepted as standard by Sanofi-Aventis.
In terms of duration of action, Novo Nordisk summarized the results from the clamp trials quoted by Sanofi-Aventis:

- Lepore *et al*: the average duration of action of Lantus was 20.5±3.7 hours with one single injection of 0.3 units/kg. The authors noted that 16 out of 20 patients who participated in the trial had an average blood glucose level under 150mg/dl at 24 hours. This meant that in 4 out of 20 patients (ie 20% of all patients) the duration of action of Lantus was above 150mg/dl, ie definitely less than 24 hours. There was no data reported in the paper about the final average blood glucose level for the other 16 patients. Novo Nordisk therefore did not know whether the glucose level had deteriorated from the predefined clamped level, which would be a clear indication of the waning effect of Lantus. However, a graph depicting plasma glucose profile in Lepore *et al* clearly indicated that there was some deterioration towards 150 mg/dl for the whole cohort.

- Porcellati *et al* (2007a): the average duration of action of Lantus was 20.2 (17.0-25.0) hours with one single injection of 0.35 units/kg and 24 (22.0-28.5) hours with an injection after achieving 'steady-state' (ie having used Lantus for 7 days). The authors did not publish the average blood glucose levels at the end of the 24-hour period (which may have indicated a waning effect), only the average blood glucose value during the 24-hour period. Nor did they report the number of patients with blood glucose levels less than or more than 150 mg/dl at the end of a 24-hour period. The investigators had only reported on the average pharmacokinetic and pharmacodynamic parameters. Thus any conclusion about the proportion of patients in whom Lantus sufficiently maintained the predefined clamped level of 7.2mmol/l (130mg/dl) could not be made.

- Porcellati *et al* (2007b): the average duration of action for Lantus at 'steady-state' (ie having used Lantus for 14 days) was 24 (23-24) hours. The investigators noted that 8% of patients, Lantus failed to maintain its metabolic effect for 24 hours.

Novo Nordisk re-emphasised that the figures above reflected the average duration of action of Lantus. Bearing in mind that insulin sensitivity was enhanced at the end of a clamp period (DeVries, 2006); the above figures might overestimate the average duration of action.

In type 1 diabetes, health professionals had to deal with an absolute lack of endogenous insulin secretion. Therefore, an overall claim of 24-hour control should reflect a duration of action covering the 24-hour period in all patients. Assuming that the duration of action of insulin glargine was dose-dependent, one could argue that with an increase in dose the 24-hour period could be covered in these patients. However, in clinical practice health professionals had to find an acceptable balance between proper metabolic control and the incidence of hypoglycaemic episodes. In those patients with type 1 diabetes who had a basal insulin

requirement less than the average, increasing the dose would result in more hypoglycaemic episodes. This could be why clinicians used Lantus twice daily in between 24.2% and 35.6% of patients with type 1 diabetes (Albright *et al*, 2004, Garg *et al*, 2004). The clinical experience should and must be considered when the duration of action of Lantus was discussed. In fact Sanofi-Aventis had acknowledged this when it stated 'the experimental model might not reflect real-life conditions of patients with type 1 diabetes'.

Novo Novartis noted that in its previous submissions it provided detailed information which made the overall 24-hour control claim questionable in type 2 diabetes as well.

Turning to the MHRA guideline, Novo Nordisk noted that Sanofi-Aventis appeared to have avoided addressing this point.

Sanofi-Aventis concluded 'In summary, the evidence presented with the initial complaint firmly demonstrated that Lantus remained effective at maintaining glycaemic control for *up to 24 hours* at doses as low as 0.3 U/kg' (emphasis added). Novo Nordisk fully agreed with Sanofi-Aventis that a claim of 'up to 24-hour duration' would more accurately reflect the properties of Lantus than the current all encompassing claim.

On the basis of the above, Novo Nordisk alleged that the '24 hour control' claim used by Sanofi-Aventis was in breach of Clauses 7.2, 7.4 and 9.1 of the Code.

Novo Nordisk noted Sanofi-Aventis' comment that it was discourteous to primary care clinicians in relation to their knowledge about the dosing of insulin. Novo Nordisk stressed that its comment had been taken out of context. Novo Nordisk agreed with the Panel that insulin dose was an important consideration and that health professionals would be well aware of this fact. The point Novo Nordisk was endeavouring to make was that data from clamp studies were difficult to translate into a clinical setting, since there was no consensus on the definition and interpretation of clamp study results amongst diabetologists.

APPEAL BOARD RULING

The Appeal Board noted that on poster LAN 07/1038 and the leavepiece the claim '24 hour glycaemic control' appeared as a strapline beneath the Lantus product logo. 'Once daily 24-hour glycaemic control' appeared in a similar position on poster LAN05/215. On the leaflet 'Once Daily 24-Hour' appeared as part of the product logo. In the patient booklet there were a number of references to Lantus working for 24 hours.

The Appeal Board noted that of the data provided in substantiation of the claims at issue, the only data available when the complaint was made was Lepore *et al*. Lepore *et al* had studied the pharmacokinetic and pharmacodynamic effects of Lantus in 20 patients using an isoglycaemic 24-hour clamp technique. The authors had thus examined duration of action of Lantus, not its efficacy in terms of glycaemic control.

In the Appeal Board's view, in the context of diabetes, 'control' referred to glycaemic control ie the maintenance of blood glucose between set parameters. The Appeal Board noted that Lantus was a basal insulin designed to provide a background, constant suppression of blood glucose. Section 5.1 of the SPC included a graph comparing the activity profile in patients with type 1 diabetes of insulin glargine and NPH insulin. The graph showed that the activity profile of insulin glargine was smooth, peakless and almost constant between 9 and 24 hours (which was when the observation period ended).

The Appeal Board noted that in response to a question, the Sanofi-Aventis representatives submitted that no type 1 diabetic would be controlled solely on Lantus and only about half of type 2 diabetics would be controlled on a combination of Lantus and oral agents. Most diabetics would thus require short-acting insulin, in addition to Lantus, to cope with daily glucose peaks resulting from meals. The Appeal Board thus considered that a once daily dosage or a 24-hour course of action for a basal insulin did not equate to 24-hour glycaemic control.

The Appeal Board considered that claims for 24-hour control or 24-hour glycaemic control were not capable of substantiation and were exaggerated and misleading in that regard. The Appeal Board ruled breaches of Clauses 7.2 and 7.4. The appeal was successful on this point. The Appeal Board did not consider that Sanofi-Aventis had failed to maintain high standards and no breach of Clause 9.1 was ruled. The appeal was unsuccessful on this point.

2 'Joe's Rough Guide to Diabetes' book

COMPLAINT

Novo Nordisk noted that this book was authored by Joseph JM Fraser and published by Wiley. The logo of Sanofi-Aventis was on the back of the publication; therefore Novo Nordisk alleged that this book was sponsored by the company. However the publication did not state the extent of the involvement of Sanofi-Aventis in this process and thus it was alleged to be in breach of Clause 9.10 of the Code.

Novo Nordisk alleged that a table of data within the book itself contained inaccurate information regarding the onset of action, the peak of action and duration of action of some insulin preparations:

- *onset of rapid-acting analogues:* the book stated 5-15 minutes however SPCs of each rapid-acting analogue stated 10-20 minutes.
- *onset and duration of action of intermediate-acting insulins:* the book stated 2-4 hours and 12-18 hours respectively however the SPC of Insulatard (Novo Nordisk's intermediate-acting insulin preparation) stated within 1½ hours and approximate 24 hours.
- *Long-acting insulins:* the book stated 24 hours of action for Lantus (neither approximately nor up to, but exactly 24 hours) while the SPC of Lantus stated *'The time course of action of insulin and insulin analogues such as insulin glargine may vary*

considerably in different individuals or within the same individual.' However in case of Levemir, which was the only direct competitor, the book stated that it started to work in 1 to 2 hours, had a peak at 6-8 hours and a duration of 6-23 hours. These claims contradicted the Levemir SPC which stated *'For doses in the interval of 0.2-0.4 U/kg, Levemir exerts more than 50% of its maximum effect from 3-4 hours and up to approximately 14 hours after dose administration' and 'maximum serum concentration is reached between 6 and 8 hours after administration'.* More importantly the SPC also stated that *'the duration of action is up to 24 hours depending on dose'.*

Novo Nordisk noted that during inter-company discussion, Sanofi-Aventis had stated that its only involvement has been to purchase copies to provide health professionals (as an educational service, not as a promotional item) and considered it as a valuable resource with considerable educational value for this audience. In this case, it would further increase the need for providing accurate, fair and balanced information. This book clearly failed to provide such basic information.

Novo Nordisk's major concern regards the fact that Sanofi-Aventis considered the content was fair and accurate and of significant educational merit when it clearly tried to highlight differences between two insulin preparations (insulin glargine and insulin detemir) that were in direct competition with each other in the market.

Based on this Novo Nordisk alleged that the book was in clear breach of the Code regarding Clauses 14.3 and 18.2 and therefore it had requested that Sanofi-Aventis withdrew this publication from distribution. Novo Nordisk queried whether the dissemination of such misleading information under the guise of an educational aide warranted the issue of a corrective statement to the recipients of this book relating to the claims/'facts' contained therein.

RESPONSE

Sanofi-Aventis submitted that neither it nor its agents had been involved in the initiation, creation, support to the author, editorial control or any other aspect of the production of this book. The publishers approached Sanofi-Aventis with the completed book to see if the company would be interested in purchasing it when it was published.

The book provided an excellent overview of the problems that adolescents might encounter in facing up to a future with diabetes, and as such was a valuable, educational resource for health professionals in order to increase their understanding of the unique aspects that teenage life introduced to diabetes care. It was therefore decided that this was appropriate to supply as an educational resource in accordance with Clause 18.2 of the Code. The email briefing sent to sales representatives regarding the booklet reflected this view.

Sanofi-Aventis was disappointed therefore that Novo Nordisk had ignored the value that this book could bring through its 42 pages of perspective on life through the eyes of a diabetic teenager, choosing instead to focus on a single point. This point was that the speed of onset of action of one class of insulins which was stated to be 5-15 minutes, compared to the SPCs which collectively described 10-20 minutes. This statement in the book was not even made in reference to an individual product, rather to a class as a whole.

Sanofi-Aventis submitted that all other information contained in this book was accurate and in accordance with the SPCs, including the detail which Novo Nordisk noted regarding Lantus and Levemir. The data was presented in a simple tabular fashion, and did not specifically highlight the differences between these two products as alleged. Contrary to the allegations, Sanofi-Aventis submitted that, on balance, this book was factual and accurate and not misleading, and that its provision was in keeping with the requirements of Clause 18.2 of the Code. It greatly helped health professionals in improving their understanding of adolescent patients' problems. Contrary to the allegations this was a positive action made in the spirit of the Code to improve patient care.

Following a request for a response to the alleged breach of Clause 14.3, Sanofi-Aventis submitted that the book was approved according to its standard procedures and as required by that clause.

PANEL RULING

The Panel noted that the back cover of the book included the Sanofi-Aventis logo and a statement 'Because health matters'. Sanofi-Aventis had no role in the initiation, creation or production of the book. It had purchased copies of the book which cost less than the maximum £6 plus VAT permitted for promotional aids. The book was aimed at teenagers with diabetes. The foreword was written by a consultant paediatrician who suggested that the book ought to be available to every young diabetic and to anybody involved in helping young people to grow up with diabetes.

The Panel considered that the purpose of the book was not entirely clear. Sanofi-Aventis' written submission stated that it was provided to health professionals to increase their understanding of teenage life with regard to diabetes care ie as an educational resource for the health professional. The representatives' briefing material stated that it was a mixture of practical advice and personal experience; a great read for anyone but was particularly relevant to adolescents and young adults. The book was part of the support the company wanted to offer to adolescent patients. It was to be used in centres dealing with high numbers of adolescents and young people. The Panel thus considered that representatives had been instructed to use the book as a gift intended for use by patients.

The Panel noted that the supplementary information to Clause 18.2 of the Code, Gifts to or for Use by Patients stated that some items distributed as promotional aids were intended for use by patients and these were not generally unacceptable provided they met the

requirements of Clause 18.2, for example, puzzles and toys for a young child to play with during a visit to the doctor. No gift or promotional aid for use by patients must be given for the purpose of encouraging patients to request a particular medicine.

With regard to the provision of books as promotional aids to health professionals, the relevant supplementary information to Clause 18.2 Gifts stated 'Certain independently produced medical/educational publications such as textbooks have been held to be acceptable gifts under Clause 18.2. The content of publications used in this way has to be considered carefully and must comply with the Code as regards any references to the donor's or competitors' products. It might be possible to give certain medical/educational publications in accordance with Clause 18.4 – Provision of Medical and Educational Goods and Services'.

The Panel noted that neither Novo Nordisk nor Sanofi-Aventis referred to Clause 18.4 of the Code.

The Panel noted that Clause 9.10 required that material relating to the medicines sponsored by a company must clearly indicate that it had been sponsored by that company. Sanofi-Aventis had purchased copies (at £1.25 per copy) to supply to health professionals.

The Panel did not know whether the book would have existed if Sanofi-Aventis had not purchased 20,000 copies to distribute as gifts. The Panel was concerned that the logo appeared on the book without a clear explanation as to Sanofi-Aventis' involvement. The Panel considered that on the information before it as Sanofi-Aventis had not contributed to the expenses of producing the book, it had not sponsored it as set out in Clause 9.10 of the Code and no breach of that clause was ruled.

The Panel examined the table of data at issue which was headed 'Insulins' and which set out the trade names for various types of insulin eg rapid acting analogue. Information was given in columns headed 'Starts To Work In', 'Peak Action' and 'Duration'. The bottom of the table stated 'Please remember these are approximate figures. Please consult your diabetes team if you want information on any particular insulin and advice as to what is the best insulin for you'.

The Panel noted Novo Nordisk's concerns about the table which generally gave a range of values for a number of insulins and clearly advocated discussion with the diabetes team. There was a direct comparison of Levemir and Lantus. The Levemir SPC stated that it was a long acting insulin analogue used as a basal insulin and that when Levemir was used as part of basal-bolus insulin regimen it should be administered once or twice daily depending on patients' needs. The duration of action was up to 24 hours. The chart in question stated that the duration of action of Levemir was '6 to 23 hours' which was not accurate. That section was the only part of the table that included information for each of the products mentioned rather than a range. The Panel queried whether the book met the requirements of the Code, particularly Clause 7.2.

The Panel noted that the only clauses cited by Novo Nordisk were 14.3 and 18.2.

The Panel did not consider that, on the information before it, the book was unacceptable either as a promotional aid for health professionals or as a gift for use by patients. Clause 18.2 of the Code required that promotional aids were inexpensive and relevant to the recipient's employment. The book was well within the cost limitation for promotional aids and relevant, and thus no breach of Clause 18.2 was ruled.

The Panel noted Sanofi Aventis' submission that the book had been approved as required by Clause 14.3 of the Code and thus ruled no breach of that clause.

Complaint received	**30 July 2007**
Case completed	**10 January 2008**

CASE AUTH/2032/11/07 NO BREACH OF THE CODE

BRISTOL-MYERS SQUIBB v NOVARTIS

Alleged disguised promotion of unlicensed medicine

Bristol-Myers Squibb alleged that ENACT (Expanding Nilotinib Access Clinical Trial), represented disguised promotion by Novartis of an unlicensed medicine. By providing inadequate written consent information for patients Novartis had not conducted itself to the high standards expected of the industry. Bristol-Myers Squibb alleged that because Novartis had misused a clinical trial as disguised promotion of an unlicensed medicine and compromised patient safety and integrity it had brought discredit upon and reduced confidence in the industry in breach of Clause 2 of the Code.

Bristol-Myers Squibb explained that the treatment of chronic myeloid leukaemia (CML) was revolutionised by the introduction of Glivec (imatinib) by Novartis over five years ago. Since this major breakthrough the problem of resistance or intolerance to Glivec had, regrettably, increased. Bristol-Myers Squibb received a marketing authorization for Sprycel (dasatinib) in November 2006, specifically for the treatment of adult CML patients who were resistant or intolerant to imatinib. Novartis was now developing nilotinib, for which it had submitted a marketing authorization application seeking a licence for the same patient population, adults who developed resistance or intolerance to imatinib. Nilotinib was a direct competitor to Sprycel.

According to the ENACT website, 'ENACT is a global access program for Nilotinib. It was created to provide early access to the drug's promising effects during the regulatory review. Eligible patients will receive Nilotinib through sites worldwide, at no cost, until it becomes commercially available'. Despite a statement on the website that the trial was intended to allow early access to CML patients 'who are either resistant or intolerant to treatment with Glivec (imatinib) *and who do not have acceptable treatment options*' (emphasis added), the study in the UK did not specify that patients had to be ineligible for Sprycel treatment before being considered for entry into this trial.

Bristol-Myers Squibb was concerned that the website displayed a promotional intent in respect of nilotinib, which was inappropriate as it was unlicensed. The title of ENACT (Expanding Nilotinib Access Clinical Trial) and the comment on the website that ENACT 'was created to provide early access to the drug's *promising effects* during the regulatory review' (emphasis added), when considered in the context of the glowing testimony to nilotinib as being 'Built on the vast knowledge and experience Novartis acquired during the development of imatinib…' created a promotional impression.

Despite the website stating that ENACT was intended for imatinib-resistant or intolerant CML patients who had no other treatment options, the fact that the selection criteria for the study ignored direct or indirect reference to Sprycel as a licensed option was further evidence that by sponsoring this trial Novartis intended to promote nilotinib.

The Panel noted that ENACT was a worldwide, multicentre, expanded access programme for Novartis' product, nilotinib. Four UK medical centres were listed on the ENACT website as actively recruiting patients. The Panel considered that the arrangements for the expanded access programme were subject to the Code.

The Panel noted that companies often provided medicines to those who had participated in clinical trials and/or other patients who might benefit from treatment before the medicine was licensed and commercially available. It was a question of whether the arrangements were reasonable. It could be argued that the expanded access programme met the definition of promotion given in the Code in that it promoted the administration of nilotinib.

It was explained on the website that the expanded access programme provided access to nilotinib to eligible patients who had no other treatment options until it was commercially available in individual countries. Individual eligibility was determined by investigators. The Panel noted Novartis' explanation that as the programme only applied to patients considered to be inappropriate for other therapeutic options, reference to resistance or intolerance to other therapies within the programme's inclusion/exclusion criteria was superfluous. The Panel noted that the programme had ethical committee approval. The Panel did not consider that Bristol-Myers Squibb had established that the ENACT programme was disguised promotion as alleged. The failure to state that UK patients had to be resistant or intolerant to Sprycel did not suffice in this regard. No breach of the Code was ruled including of Clause 2.

Bristol-Myers Squibb Pharmaceuticals Limited complained about a number of activities undertaken by Novartis Pharmaceuticals UK Ltd. A number of queries and issues were raised including whether the requirements of Paragraph 5.2 of the Constitution and Procedure had been met and whether a prima facie case had been established.

The only allegation to be considered by the Panel related to ENACT (Expanding Nilotinib Access Clinical Trial) constituting disguised promotion.

COMPLAINT

Bristol-Myers Squibb alleged that ENACT represented disguised promotion of an unlicensed medicine in breach of Clauses 10.1 and 3.1 of the Code. By providing inadequate written consent information for patients Novartis had not conducted itself to the high standards expected of the industry in breach of Clause 9.1. The misuse of a clinical trial as disguised promotion of an unlicensed medicine and the compromising of patient safety and integrity led Bristol-Myers Squibb to conclude that Novartis had brought discredit upon and reduced confidence in the industry in breach of Clause 2.

Background to the therapy area and its treatment

The treatment of chronic myeloid leukaemia (CML) was revolutionised by the introduction of Glivec (imatinib) by Novartis over five years ago. One of the noticeable elements associated with the introduction of imatinib was the great increase in the cost of treating CML, with consequent severe pressure on budgets within NHS oncology services.

Since this major breakthrough in the management of CML, the problem of resistance or intolerance to imatinib had, regrettably, increased. Bristol-Myers Squibb received a marketing authorization for its product Sprycel (dasatinib) in November 2006. Sprycel was specifically licensed for the treatment of adult CML patients who were resistant or intolerant to imatinib.

Novartis was developing nilotinib, for which it sought a marketing authorization for the same patient population, adults who developed resistance or intolerance to imatinib. Nilotinib was a direct competitor to Sprycel.

Background to ENACT

The ENACT website stated, 'ENACT is a global access program for Nilotinib. It was created to provide early access to the drug's promising effects during the regulatory review. Eligible patients will receive Nilotinib through sites worldwide, at no cost, until it becomes commercially available'. Despite the statement on the website that the trial was intended to allow early access to CML patients 'who are either resistant or intolerant to treatment with Glivec (imatinib) **and who do not have acceptable treatment options**' (emphasis added), the study in the UK did not specify that patients had to be ineligible for Sprycel treatment before being considered for entry into this trial.

Disguised promotion of an unlicensed medicine

Bristol-Myers Squibb was concerned that the website displayed a promotional intent in respect of nilotinib, which was inappropriate given its unlicensed status. The very title of ENACT (Expanding Nilotinib Access Clinical Trial) and the comment on the website, that ENACT 'was created to provide early access to the drug's **promising effects** during the regulatory review' (emphasis added), when considered in the context of the glowing testimony to nilotinib as being 'Built on the vast knowledge and experience Novartis acquired during the development of imatinib…' created a promotional impression.

Despite the website statement that ENACT was intended for imatinib-resistant or intolerant CML patients who had no other treatment options, the fact that the selection criteria for the study ignored direct or indirect reference to Sprycel as a licensed option was further evidence that by sponsoring this trial Novartis intended to promote nilotinib. If this clinical trial was truly for patients 'who do not have (an) acceptable treatment option', then one would have expected the selection criteria to include an entry criterion such as 'has the patient failed treatment on licensed treatments for patients with imatinib resistance or intolerance'. This would then have meant that patients with imatinib resistance or intolerance would have had to have had failed on Sprycel before being considered for ENACT since Sprycel was the only licensed option for such patients.

Accordingly, Bristol-Myers Squibb alleged ENACT represented disguised promotion of an unlicensed medicine and in breach of Clauses 10.1 and 3.1.

The misuse of a clinical trial as disguised promotion of an unlicensed medicine led Bristol-Myers Squibb to conclude that Novartis had brought discredit upon and reduced confidence in the industry, in breach of Clause 2.

RESPONSE

Novartis was profoundly disappointed that Bristol-Myers Squibb should have made these formal allegations after assuring Novartis through inter-company dialogue that its response was satisfactory and that Bristol-Myers Squibb considered the matter closed. To proceed in this manner displayed a disregard for the value of inter-company dialogue and directly contradicted assurances that Bristol-Myers Squibb wished to foster a cordial and candid relationship between the companies where concerns such as these could be discussed and resolved. It appeared that Bristol-Myers Squibb's actions in this matter, together with those associated with a second complaint which Novartis had considered resolved through inter-company dialogue were motivated by a complaint made to the Authority about the promotion of Sprycel. However unlike Bristol-Myers Squibb, Novartis had brought to the attention of the Authority only those matters for which no inter-company agreement could be reached. Such behaviour and the inflammatory language used by Bristol-Myers Squibb was contrary to the spirit of cooperation and self-regulation which underlayed the Code and seriously compromised any future possibility of inter-company dialogue.

Novartis did not accept that it had breached the Code.

Novartis provided print outs of the whole site and noted that there was a clear disclaimer on entering the site which confirmed that:

> *'This is a global website for ENACT (Expanding Nilotinib Access in Clinical Trials) information. The information you requested is intended for healthcare professionals only. Information on this site is not country-specific and may contain information that is different from the regulatory requirements, legal requirements or medical practices in the country in which you are located.'*

In addition, every page also carried a statement that:

> *'The compound Nilotinib described in this Website is an investigational drug. Efficacy and safety have not been established.'*

> *'There is no guarantee that Nilotinib will become commercially available.'*

Therefore this website was quite clearly both non-promotional and also not specifically targeted to a UK audience. Following inter-company dialogue Novartis asked its global teams (who managed the website) to remove reference to any UK sites from the listing, in the spirit of inter-company cooperation. Once again, Novartis was assured that this action would allay any remaining concerns that Bristol-Myers Squibb might have.

In response to the specific allegation regarding the study entry criteria listed on the web page, as explained above, the study was an expanded access programme and so only applied to patients considered by their doctor to be inappropriate for other therapeutic options. Therefore, there was no need to refer to resistance or intolerance to other therapies (including dasatanib) within the inclusion/exclusion criteria.

In summary Novartis did not consider that the allegations were supported by the evidence cited, nor did it accept that its activities had compromised patient safety or brought discredit upon or reduced confidence in the industry. It therefore strongly rejected the allegation of a breach of Clause 2.

Novartis submitted that ENACT followed the required regulations and was reviewed and approved by an ethics committee. Similar expanded access programmes had been run by other companies including Bristol-Myers Squibb.

PANEL RULING

The Panel noted that ENACT was a worldwide, multicentre, expanded access programme for Novartis' product, nilotinib. Four UK medical centres were listed on the ENACT website as actively recruiting patients. The Panel considered that the arrangements for the expanded access programme were subject to the Code.

The Panel noted that companies often provided medicines to those who had participated in clinical trials and/or other patients who might benefit from treatment before the medicine was licensed and commercially available. It was a question of whether the arrangements were reasonable. It could be argued that the expanded access programme met the definition of promotion given in Clause 1.2 in that it promoted the administration of nilotinib.

It was explained on the website that the expanded access programme provided access to nilotinib to eligible patients who had no other treatment options until it was commercially available in individual countries. Individual eligibility was determined by investigators at participating cancer care centres based on established medical criteria. The Panel noted Novartis' explanation that as the programme only applied to patients considered by their doctors to be inappropriate for other therapeutic options there was no need to refer to resistance or intolerance to other therapies within the programme's inclusion/exclusion criteria. The Panel noted that the programme had ethical committee approval. The Panel did not consider that Bristol-Myers Squibb had established that the ENACT programme was disguised promotion as alleged. The failure to state that UK patients had to be resistant or intolerant to Sprycel did not suffice in this regard. No breach of Clause 10.1 was ruled. It thus followed there was no breach of either Clause 9.1 or 2.

Complaint received	**8 August 2007**
Case completed	**15 January 2008**

CASE AUTH/2037/8/07

PRIMARY CARE TRUST PHARMACEUTICAL ADVISER v TEVA

Promotion of Qvar

The pharmaceutical adviser to a primary care trust (PCT) complained about what had been said by the medical director of Teva at an educational meeting organised by the company. Teva marketed Qvar, a CFC-free beclometasone (BDP) inhaler.

The complainant noted that the discontinuation of Becotide (BDP inhaler) by GlaxoSmithKline and the planned phasing out of CFC-containing BDP inhalers had caused a number of problems in recent months. The launch of Clenil Modulite by Trinity-Chiesi the second CFC-free BDP inhaler on the market had further escalated this problem.

The complainant stated that the problems were currently; the lack of guidance and information of when CFC-BDP would cease to be available, there was no clear guidance of when to switch to CFC-free BDP inhalers; the potency difference between Qvar and Clenil Modulite. Qvar was approximately twice as potent as Clenil and thus CFC-free prescribing required prescribing by brand (it was potentially hazardous if patients received the wrong inhaler); the fact that Qvar was not licensed for use in children under 12 years of age.

The complainant was concerned that at the meeting Teva's medical director had emphasised the following: a requirement to switch to CFC-free BDP due to the phase out of Becotide/Becloforte (this was not currently a requirement) and that there was now no choice but to switch to Qvar or Clenil. This was inaccurate as generic CFC-BDP was still available.

However, the speaker had not referred to the continued availability of generic CFC-BDP, which was quite clearly still a treatment option for patients, or the fact that Qvar was not licensed for use in children. This was a concern when the company was encouraging a therapeutic switch.

The complainant alleged that it was inappropriate and potentially hazardous to patients for a company to encourage a switch to its product when the meeting was advertised as an educational meeting. It was also inappropriate and potentially hazardous to patients, for a company to encourage a switch to a product without highlighting the licensing limitations for children. In response to a question about the licensing, the medical director stated that the issue was with the Medicines and Healthcare products Regulatory Agency (MHRA) and would be licensed imminently. This was speculation and by no means guaranteed, and such information should not be shared in a meeting of health professionals; such a forum should be for factual information and not speculation.

The complainant stated that in response to a question about generic CFC-BDP, the medical director explained that he was unsure of the continued availability of CFC gases and that he did not believe that supplies would exceed 12 months. He also actively discouraged this course of action, which again was inappropriate for this forum. Teva currently marketed CFC-BDP inhalers and the medical director should be in a better position to provide all the information that was required of him, as opposed to providing information that was favourable for the promotion of Qvar. Any discontinuation of a product should require a minimum notice period.

The Panel noted that at the meeting at issue, 'How to Improve Asthma in General Practice', the title of the medical director's presentation was 'Implications of the CFC phase out and the introduction of Beclomethasone CFC Free Alternatives'. The Panel did not accept Teva's submission that the presentation was not promotional. In the Panel's view, although there was an educational content it nonetheless promoted Qvar.

The Panel noted Teva's submission regarding the continued availability of generic CFC-BDP which, although a theoretical possibility, did not appear to be a long-term practical solution to the discontinuation of Becotide/Becloforte. According to Teva no company had applied for a CFC gas allocation in 2008 and so CFC-BDP was expected to be exhausted sooner rather than later. In any event, Teva had submitted that it was unlikely that the current manufacturers of CFC-BDP would be able to fill the gap left by Becotide/Becloforte. Clinicians had no choice but to eventually switch to CFC-free BDP. There was no set date when CFC-BDP would no longer be available. The Panel considered that, in the context of a presentation about the implications of CFC phase out, it was not necessarily misleading to encourage health professionals to plan ahead for a time when CFC-BDP would no longer be available. No breach of the Code was ruled.

The Panel noted that the medical director did not state in his presentation that, unlike Becotide, Qvar was not licensed for use in children under 12. Although, according to Teva, less than 15% of asthmatics were under 12 years of age, this group would nonetheless present clinicians with important practical and clinical considerations as they planned to switch patients to CFC-free BDP. In that regard the Panel considered that, in the context of the presentation at issue, the omission of such information was misleading. A breach of the Code was ruled.

According to the complainant, he had asked the medical director about the use of Qvar in children and received the reply that the issue was with the MHRA and the product would be so licensed imminently. Teva submitted that the medical director had referred to the need to conduct a growth study and that results from that would not be due until the second half of 2008 and following this a paediatric licence would be expected in a short period of time. When asked for more information the medical director had stated that the timing of the regulatory process was not something that could be shared. The medical director had stated that Teva anticipated a successful application process with appropriate timings as Qvar was licensed for use in children in 10 European countries. Nonetheless, the Panel noted that its ruling above that it was misleading not to mention that Qvar was not licensed for children below the age of 12.

The Panel was concerned that the complainant appeared to have been left with the impression that the change in licence to allow paediatric use was imminent. Teva had submitted that it expected the licence to be granted shortly after the completion of the paediatric growth study which was due in the second half of 2008. There appeared to be a difference of opinion.

The answer given to the complainant was in response to an unsolicited enquiry. There was no evidence to show that on the balance of probabilities the answer was not factual and accurate, or that it was either misleading or promotional. The answer could thus take advantage of one of the exclusions to promotion. The Panel did not consider that in this regard Qvar had been promoted for use in children. No breach of the Code was ruled.

The pharmaceutical adviser to a primary care trust (PCT) complained about a meeting organised by Teva UK Limited. Teva marketed Qvar, a CFC-free beclometasone (BDP) inhaler.

COMPLAINT

The complainant noted that the discontinuation of Becotide (a CFC-containing BDP inhaler) by GlaxoSmithKline and the planned phasing out of CFC-containing BDP inhalers had caused a number of problems in recent months. The launch of Clenil Modulite by Trinity-Chiesi the second CFC-free BDP inhaler on the market had further escalated this problem.

The complainant stated that the problems were: currently: the lack of guidance and information of when CFC-BDP would cease to be available, there was no clear guidance of when to switch to CFC-free BDP inhalers; the fact that Qvar was approximately twice as potent as Clenil and thus CFC-free prescribing required prescribing by brand (it was potentially hazardous if patients received the wrong inhaler), and the fact that Qvar was not licensed for use in children under 12 years of age.

The complainant had been concerned about Teva's activities for some time and had tried to deal with the matter locally in the past, as to his knowledge Teva had not broken ABPI rules. In a previous post the complainant had spoken to the marketing manager at length over Teva's sponsorship of a local guidelines meeting.

The complainant had a number of concerns about an educational meeting he had attended in August 2007. The meeting had two speakers, a chest physician and the medical director of Teva.

The complainant was concerned that the latter had emphasised a requirement to switch to CFC-free BDP due to the phase out of Becotide/Becloforte (this was not currently a requirement) and stated that there was now no choice but to switch to Qvar or Clenil. This was inaccurate as generic CFC-BDP was still available.

However, the speaker had not referred to the continued availability of generic CFC-BDP, which was quite clearly still a treatment option for patients and the fact that Qvar was not licensed for use in children. This was a concern when the company was encouraging a therapeutic switch.

The complainant alleged that it was inappropriate and potentially hazardous to patients for a company to encourage a switch to its product when the meeting was advertised as an educational meeting. It was also inappropriate and potentially hazardous to patients, for a company to encourage a switch to a product without highlighting the licensing limitations for children. In response to a question about the licensing, the medical director stated that the issue was with the Medicines and Healthcare Products Regulatory Agency (MHRA) and would be licensed imminently. This was speculation and by no means guaranteed, and such information should not be shared in a meeting of health professionals; such a forum should be for factual information and not speculation.

The complainant stated that in response to a question about generic CFC-BDP, the medical director explained that he was unsure of the continued availability of CFC gases and that he did not believe that supplies would exceed 12 months. He also actively discouraged this course of action, which again was inappropriate for this forum. Teva currently marketed CFC-BDP inhalers and the medical director should be in a better position to provide all the information that was required of him, as opposed to providing information that was favourable for the promotion of Qvar. Any discontinuation of a product should require a minimum notice period.

When writing to Teva, the Authority asked it to respond in relation to Clauses 3.2, 7.2, 7.4, 9.5 and 2.

RESPONSE

Teva was disappointed that a complaint had been made to the Authority as it appeared that in this instance a company could make a verbal statement that was not acceptable to an individual health professional in response to a question in an open forum and

someone could complain without determining the factual position. This complaint related to the questions and statements made by the complainant and not the content of the presentation itself.

Teva was also very disappointed in the complainant's behaviour as it was clear from his questions to the medical director that he required a more detailed discussion, so the medical director offered to continue these discussions with him in private after the public session was concluded. Unfortunately this was not possible as the complainant left immediately after the question session. This was most regrettable as some of the misconceptions included in the complaint could have been answered there and then.

Teva submitted that following the launch of Clenil it had worked closely with the Department of Health (DoH) and the MHRA to try to ensure effective and consistent communication to health professionals to minimise any confusion between products and to ensure appropriate actions were taken. This was because generic prescriptions of CFC-free BDP could potentially result in patients receiving an incorrect dose of BDP as Qvar and Clenil had different relative potencies. Following this realisation Teva conducted market research amongst pharmacists and following submission of these data, the MHRA recommended, in August 2006, that both Clenil and Qvar should be prescribed by brand. Following this, and during Teva's medical director's meetings with health professionals during 2007 it had become increasingly clear that there was limited understanding of the phase out of products containing CFCs and the potential availability of product following the discontinuation of Becotide and Becloforte announced in October 2006.

Teva was very concerned by this low level of awareness and understanding of the situation in general and so it had worked very closely with the MHRA and DoH to determine the best way to communicate with health professionals particularly now that Becotide and Becloforte were no longer available. It was confirmed in a meeting between Teva, the MHRA and the DoH that no company had applied for a CFC allocation for 2008 with the clear implication that products containing CFCs would be exhausted in the early part of 2008. In addition Teva confirmed that some of the components for the inhalers were also in short supply as manufacturing had ceased some time ago.

At this meeting Teva predicted that its product Beclazone MDI would be exhausted in March 2008 and potentially sooner if there was increased demand. Teva estimated that Beclazone Easi-Breathe could be exhausted approximately 12 months later but once again this would be sooner if an increased demand for this product was seen after Becotide was discontinued. This data was contained in the slide presentation made in August which was provided together with the email confirming that it was presented and sent to the above agencies.

It was agreed by all attendees that Teva should increase its educational activities, which included speaker meetings to try to increase health professionals' understanding and awareness of this issue. This was supported by all agencies present. Teva agreed to meet again in September to assess the impact of the Becotide/Becloforte withdrawal during August.

Teva noted that the complainant stated that the planned phase out of CFC-BDP inhalers had caused a number of problems in recent months and that the launch of Clenil Modulite, the second CFC-free BDP on the market, had further escalated this problem. Teva was unaware of any problems in the market place, and as neither of the actions highlighted in this paragraph had been implemented by Teva it did not see that they were relevant to a complaint against it.

Teva noted the complainant's comments that the current problems were:

- Lack of guidance and information. – Teva agreed that this was currently lacking, but guidance could only be given by the MHRA, the DoH and NHS management. Teva had attempted to influence these organisations but it was not within its power to provide guidance to NHS managers in any capacity.

- The 2:1 potency differential between Qvar and Clenil although Teva could not agree that this was a problem as both were administered with the same puff pattern to patients. If the MHRA guidance was followed and the products were prescribed by brand there was no danger of patients receiving the wrong product and this was what the MHRA letter of August 2006 recommended.

- The fact that Qvar was not licensed for use in children younger than 12 years although again Teva did not agree that this was a problem as currently many products were available for use in these children, including Beclazone which was available as an MDI, Autohaler and Easi-Breathe device.

Teva noted that the complainant had been concerned about its activities for some time and had previously tried to deal with the matter locally although to his knowledge Teva had not broken ABPI rules. He also claimed to have spoken to Teva's marketing manager. Teva stated that it had not received any formal complaints from the complainant before this one, and if, as he stated that no ABPI rules were broken, then it submitted that his statement of concern was inappropriate.

In addition Teva confirmed that its marketing manager had not spoken to the complainant; the complainant had interacted with the sales manager in his previous post.

Teva noted the complaint relating to the presentation (provided) by its medical director. This presentation was in three sections:

- The market and costs associated with prescription

of asthma medicines and the provision of healthcare for asthma patients. These data were derived from reputable sources and were correct. These discussions were paramount for the understanding of the transition because if patients were transferred on to more expensive products such as combinations then there would be significant increases in cost to the NHS.

- A review of some of the long-term clinical data for Qvar to make the point that not all BDP formulations had the same effect in patients and this needed to be considered by health professionals when they prescribed products. No long-term clinical studies with Clenil were discussed as no studies had been conducted with end points of symptom free days and quality of life assessments. This had been confirmed in writing by Trinity-Chiesi and copies of these letters had been previously submitted to the committee. Additional copies could be supplied upon request.

- The requirements to prescribe CFC-BDP by brand as the history of these types of guidance had not been well understood by health professionals.

At the end of the presentation the Qvar prescribing information was displayed and summaries of product characteristics (SPCs) were available on request. There was no mention of special patient groups, use outside licence, or dosing etc, as this was not appropriate to the subject and therefore none of the matters contained in the complaint were included in the presentation.

Teva submitted that the subject and content was chosen as this was a subject that was currently under discussion locally and the chairman agreed that there needed to be a greater understanding of the situation so that patients could be managed appropriately in a potential move to CFC-free alternatives. The presentation was clearly structured and was educational in content as defined by addressing a subject of which the audience had little knowledge. Teva therefore submitted that this was not a promotional presentation and was appropriately delivered by its medical director.

Teva noted that the complainant had requested clarification stating that Qvar was not licensed in children under the age of 12 in contrast to Clenil which was so licensed. Teva's medical director agreed that Qvar was not licensed in children and also stated that the complainant's statement that Clenil was licensed in children under the age of 12 was misleading. The medical director answered each part of the question as follows:

Qvar paediatrics – At the meeting with the MHRA in August, Teva's medical director agreed to conduct a growth study as requested and a clinical research organisation had already been selected, a protocol had been written and Teva expected to enrol the first patients in early 2008 with results in the second half of 2008. After that Teva would expect a registration in the UK in a short period of time. Currently the Qvar MDI was approved for use in children in the US and in 10 European countries.

Teva's medical director however stated that Teva anticipated a successful application process with appropriate timings as Qvar was licensed for use in children in 10 European countries. When further pressed by the complainant for additional information, Teva's medical director had stated that this was not possible as the timing of the regulatory process was not something that could be shared.

To ensure a balanced answer Teva's medical director also corrected the complainant's statement that Clenil was licensed for use in children under 12 years of age. Teva's medical director had stated that Clenil was only licensed for use in children under the age of 15 years when using a Volumatic spacer, therefore he suggested that this should be communicated whenever the use of Clenil in children was discussed. Teva's medical director also stated that he had confirmed that this was correct with the MHRA at a recent meeting.

Teva's medical director completed the answer to be fair and balanced by stating that CFC products such as Beclazone MDI, Beclazone Easi-Breathe, Airomir and Aerobec Autohaler were also approved for use in children.

The complainant then asked when Teva would be phasing out Beclazone as this was not yet a requirement under the Montreal Protocol. Teva's medical director's response was the same as that provided to the MHRA and DoH ie at current market usage Beclazone MDI would cease to be available in March 2008 or sooner if there was an increase in demand following the withdrawal of Becotide. Teva was currently re-evaluating the situation and, as stated to the meeting, once this was defined it would communicate the revised information to the chairman for dissemination to the audience. At the meeting Teva's medical director stated that Teva hoped to be able to supply Beclazone Easi-Breathe for a further 12 months after the MDI but once again this depended on whether there was an increase in demand.

The complainant responded that generic products would take up the volume from Becotide and Beclazone. Teva's medical director stated that Beclazone and Becotide represented 80% of the BDP market and only three low volume suppliers were unaccounted for and it was very unlikely that they could supply such a large increase in volume due to their own supply constraints, and as no company had applied for a CFC allocation for 2008 there was no indication that any product of significant size was about to replace CFC-BDP demand and satisfy the current level of generic prescriptions. Therefore once Becotide and Becloforte were discontinued it was likely that they would accelerate the use of remaining stocks of other CFC-BDP products.

When the complainant asked Teva's medical director to be more specific he indicated that Teva would not be able to provide a better estimate until after 10 September and he offered to email or talk to him as soon as this was clear. The complainant did not take up this offer.

The complainant then thanked Teva's medical director for the reply which he took to mean that he agreed; the medical director expected to receive his email address after the meeting, and was therefore surprised to find that the complainant had left without any communication or contact.

Teva's response to some of the complainant's statements were:

A requirement to switch to CFC-free due to the phase out of Becotide/Becloforte (this was not currently a requirement)

Teva submitted that although CFC-BDP therapy had not been reclassified to non-essentiality and thus officially commence a phase out of CFC-BDP, there would be a need to evaluate patients as supplies would no longer satisfy market demand. In view of the time taken to review patients it seemed prudent for physicians and PCTs to develop their plans before product availability was decreased.

Teva concluded that although the statement was correct in the light of the Montreal Protocol it did not reflect the current UK situation as it failed to take into account product availability.

The speaker emphasised that there was now no choice but to switch to CFC-free and the options were Clenil or Qvar. This was inaccurate as generic CFC-BDP was still available

Teva submitted that until recently this statement would have been correct with approximately 50% of CFC-BDP prescriptions satisfied by the Becotide range of products and 30% by the Beclazone range. However, as had been outlined above once these products were exhausted there would not be sufficient replacement products as only three low volume suppliers would remain. Therefore when these products were exhausted patients would need to move to CFC-free alternatives. Clearly there were a number of these options available and were not limited to just Qvar and Clenil.

Teva submitted that generic CFC-BDP was therefore not a long-term option for significant prolongation as insufficient product would be available. Teva therefore regarded the complainant's comment as incorrect and as the answers given by Teva's medical director were factually correct it did not believe that it breached the Code in any way.

There was no mention of continued generic CFC-BDP

Teva submitted that this had been covered above

There was no mention of the fact that Qvar was not licensed in children

Teva submitted that the presentation was about the discontinuation of CFC-BDP and no discussions or claims were made relating to the use of any product in special patient groups. Once again Teva failed to see why the lack of a paediatric licence was a concern for the complainant as Qvar was appropriate therapy for patients aged ≥12 years ie more than 85% of asthmatics. Indeed if minority groups were to be assessed and discussed a totally different lecture would have been required.

Teva submitted that in addition as required by the Code, had any further information been required, the prescribing information was shown on the last slide and its medical director would have happily discussed this with any of the delegates on request, and he confirmed that the SPC was available at the meeting.

It was inappropriate to encourage a switch to the sponsor's product when the meeting was advertised as an educational meeting

Teva submitted that the purpose of an educational meeting was to impart knowledge to an audience of which they previously had little information. The presentation contained significant data regarding the phase out of CFCs and was well received by the audience and the chairman found the content most interesting. Teva's medical director did not advocate a switch to Qvar as this would have been clearly inappropriate, he did however indicate that, in the next six months or so, patients receiving CFC-BDP would need to have their therapy reviewed and changed to a CFC-free alternative. Teva's medical director did not advocate a switch to Qvar but he did contend that UK health professionals now needed to consider the therapeutic strategies as availability of CFC-BDP would decline rapidly.

Paediatric licence

Teva failed to understand the complainant's comment relating to the paediatric indication on several accounts. Firstly as stated before, Teva's medical director did not suggest that a licence would be granted imminently. Secondly, as the product was already licensed in children below 12 in ten European countries and also in the US it would be very unusual if Teva was unable to obtain approval in the UK – although no guarantee could be given. Teva would follow the process agreed with the MHRA and conduct the paediatric growth study, after which it had every confidence that a licence would be granted.

Teva submitted that as the reply was given in response to questions from the complainant it clearly was not a promotional message and as the statement was factually correct and reflected agreements with the MHRA it did not contravene the Code.

Paediatric therapies within the presentation

Teva submitted that this was a short presentation relating to the phase out of CFC-BDP and it was not appropriate to discuss special patient populations and unlicensed indications such as doses in children.

Teva submitted that if its medical director had included children he would have had to discuss not only Qvar but also the issues relating to Clenil having a licence in children less than 15 years (not the 12 years

for Qvar as was the usual age in the asthma therapeutic guideline in the UK and US) and that Clenil was only approved for use in this group when prescribed with a Volumatic spacer. To discuss these details and other important differences between the products would have required a totally different presentation and this was not the subject of the meeting.

Teva submitted that its medical director was, however, able to provide factual answers to the complainant's questions and therefore rejected that these answers were speculative as claimed.

They were based on sound agreements with the MHRA and clinical research organizations and the details of the clinical trial programme that were discussed with the audience were as agreed with the MHRA. Teva submitted that it was appropriate to respond to questions in this factual manner as it was an educational meeting and indeed if its medical director had failed to do so Teva expected the complainant would have called him evasive. Teva therefore submitted that the presentation could not be regarded as promotional and this and the answers to this question did not breach the Code.

Switch of patients to Qvar

Teva submitted that its medical director did not state that products would have to be switched but he did state that if there was no CFC-BDP product available then alternative strategies would need to be employed and owing to the large number of patients, and manufacturing lead times, it was now time to consider those options. Although the complainant would like to believe that generic CFC-BDP would remain a viable alternative it was simply not the case and owing to the large number of patients any remaining CFC-BDP supplies were likely to be exhausted sooner than expected.

Teva's medical director had agreed that it would communicate the position as soon as it could define it after 10 September when August data would be available. The position had not changed and Teva would be communicating with the chairman of the meeting as agreed.

Discontinuation of products in the UK

Teva agreed with the complainant's comments about a minimum period. The period of notification required was only 3 months and there was no specific requirement to notify the market any sooner. Teva therefore had no requirement at present to formally notify the heath professions until December 2007.

Meeting audience

Teva submitted that the meeting was attended by 96 local health professionals (56 general practitioners, 29 nurses, 4 hospital doctors and 7 PCT and managerial staff) which was an indication that the subject of the meeting was of great interest.

Review of the specific clauses of the Code

Teva submitted that the meeting was well balanced and the presentations were accurate and the questions were answered accurately and factually, it therefore denied a breach of Clause 2.

No unsolicited mention was made of any unauthorised indications in the educational presentation. When Teva's medical director was questioned about the paediatric licence the responses were accurate and reflected the company's agreement with the MHRA following its meeting in August. Teva therefore denied a breach of Clause 3.

All data already presented to the MHRA, DoH and the costs and market data in the presentation were derived from Teva's recent submission to the National Institute for Health and Clinical Excellence (NICE) health technology assessment. Teva therefore submitted that all data were validated and correct; none of the information provided at the meeting was in breach of Clause 7.2.

Teva submitted that the comparisons made were from data contained in the relevant SPCs for Qvar, Clenil and Becotide and were therefore correct. The comparison therefore did not breach Clause 7.4.

Teva submitted that the presentation was detailed, contained data that the audience had not seen before and provided up-to-date and accurate information about the CFC phase out and prescribe by brand recommendations from the MHRA for CFC-free products. All questions were answered factually with data that had already been agreed with the MHRA and DoH and no misleading or evasive statements were made. Teva therefore submitted that the meeting upheld high standards. The company thus denied a breach of Clause 9.1.

Conclusion

Teva was very disappointed that the complainant had complained in this manner without establishing whether his beliefs or claims were credible and correct. The company was also concerned that the complainant had based his complaint on answers given in response to his own questions. The responses accurately reflected validated data presented to two government agencies and were therefore correct.

Teva therefore concluded that:

- The presentation given by Teva's medical director was educational in content and was fair, balanced and appropriate for the audience that attended
- The audience was appropriate and consisted of health professionals
- The situation reflecting CFC phase out was accurately stated
- The process by which Teva expected to receive regulatory approval in the UK was accurately stated and the audience was not led to believe that it was imminent as it was stated that the study would end in the second half of 2008 and this was a necessary step before any licence could be granted.

Teva submitted that neither the meeting nor any of the answers to the complainant's questions breached any of the clauses of the Code including Clauses 2, 3.2, 7.2, 7.4 and 9.1.

PANEL RULING

The Panel noted that the meeting at issue, 'How to Improve Asthma in General Practice', which had been sponsored by Teva, featured two speakers one of whom was the medical director for Teva UK Ltd. The title of the medical director's presentation was 'Implications of the CFC phase out and the introduction of Beclomethasone CFC Free Alternatives'. A copy of the presentation, with notes, was provided.

The Panel noted Teva's comments that the complaint concerned questions and statements made by the complainant and not the content of the presentation. The Panel did not consider that it was necessarily unacceptable to make a complaint on this basis. The questions had arisen as a result of material included or not included in the presentation.

The Panel did not accept Teva's submission that the medical director's presentation was not promotional. In the Panel's view, although there was an educational content it did promote the prescription, supply, sale or administration of Qvar and thus met the definition of promotion (Clause 1.2 of the Code). The presentation concluded with a slide showing the Qvar prescribing information.

The Panel noted Teva's submission regarding the continued availability of generic CFC-BDP, which although a theoretical possibility, did not appear to be long-term practical solution to the discontinuation of Becotide/Becloforte. According to Teva no company had applied for a CFC gas allocation in 2008 and so CFC-BDP was expected to be exhausted sooner rather than later. In any event, Teva had submitted that it was unlikely that the current manufacturers of CFC-BDP would be able to fill the gap left by Becotide/Becloforte. Clinicians had no choice but to eventually switch to CFC-free BDP. There was no set date when CFC-BDP would no longer be available. According to Teva's presentation the company anticipated that over the next few years only CFC-free products and dry powder devices would be permitted. The Panel considered that, in the context of a presentation about the implications of CFC phase out, it was not necessarily misleading to encourage health professionals to plan ahead for a time when CFC-BDP would no longer be available. No breach of Clauses 7.2 and 7.4 was ruled.

The Panel noted that the medical director did not state in his presentation that, unlike Becotide, Qvar was not licensed for use in children under 12. Although, according to Teva, less than 15% of asthmatics were under 12 years of age, this group would nonetheless present clinicians with important practical and clinical considerations as they planned to switch patients to CFC-free BDP. In that regard the Panel considered that, in the context of the presentation at issue, the omission of such information was misleading. A breach of Clause 7.2 was ruled.

The Panel noted that, according to the complainant, he had asked the medical director about the use of Qvar in children and received the reply that the issue was with the MHRA and the product would be so licensed imminently. Teva submitted that the medical director had referred to the need to conduct a growth study and that results from that would not be due until the second half of 2008 and following this a paediatric licence would be expected in a short period of time. When asked for more information the medical director had stated that the timing of the regulatory process was not something that could be shared. The medical director had stated that Teva anticipated a successful application process with appropriate timings as Qvar was licensed for use in children in 10 European countries. Nonetheless, the Panel noted that its ruling above that it was misleading not to mention that Qvar was not licensed for children below the age of 12 and that the use of Qvar in children was discussed in response to an unsolicited enquiry.

The Panel was concerned that the complainant appeared to have been left with the impression that the change in licence to allow paediatric use was imminent. Teva had submitted that it expected the licence to be granted shortly after the completion of the paediatric growth study which was due in the second half of 2008. There appeared to be a difference of opinion.

The Panel considered that the answer given to the complainant was in response to an unsolicited enquiry. There was no evidence to show that on the balance of probabilities the answer was not factual and accurate, or that it was either misleading or promotional. The answer could thus take advantage of one of the exclusions to promotion given in Clause 1.2 of the Code. The Panel did not consider that in this regard Qvar had been promoted for use in children. No breach of Clause 3.2 was ruled.

The Panel noted its rulings above and did not consider that overall high standards had not been maintained. No breach of Clause 9.1 was ruled. The Panel did not consider that the matter warranted a ruling of a breach of Clause 2 of the Code which was a sign of particular censure and reserved for such use.

Complaint received 17 August 2007

Case completed 30 October 2007

CASE AUTH/2038/8/07

NOVO NORDISK v SANOFI-AVENTIS

Promotion of Lantus

Novo Nordisk complained about a Lantus (insulin glargine) mailing sent by Sanofi-Aventis. Novo Nordisk had a competitor product, Levemir (insulin detemir).

Novo Nordisk alleged that a cost comparison claim 'Lantus offers a significant cost advantage over insulin detemir in both type 1 and type 2 diabetes' followed by two bullet points which claimed that Lantus treatment costs were 10% lower and 28% lower (p<0.001) in type 1 and type 2 diabetes respectively, than for insulin detemir, was in breach of the Code. The Poole *et al* reference clearly emphasised that there was a significant difference between the two products in terms of the applied insulin regimens in type 2 diabetes; like had not been compared with like. The more frequent use of basal plus oral regimen with Lantus thus related to lower costs therefore the overall claim about the reduced treatment-related costs in type 2 diabetes was unfair and misleading. Furthermore during the analysed period Levemir did not have a marketing authorization for basal plus oral indication and was used off-label. The Code stated that an economic evaluation must be consistent with the marketing authorization, therefore using Poole *et al* for promotional claims was in breach of the Code.

The Panel noted that the mailing was entitled 'Which basal insulin analogue has lower anti-diabetic prescribing costs compared with Levemir in similar patients?' Beneath 'Once-daily Lantus' it continued 'Evidence from a retrospective database analysis of routine general practice of people with diabetes being initiated on basal insulin therapy'. Page 2 was headed 'Lantus offers a significant cost advantage over Levemir in both type 1 and type 2 diabetes'.

Pages 1 and 2 were referenced to Poole *et al* which compared the costs of diabetes treatments, administration and monitoring following initiation of treatment with glargine or detemir regimens in type 1 or type 2 diabetes mellitus patients, using a database of UK patients treated in general practice. The study showed that prescribing costs were significantly lower in patients treated with glargine than those treated with detemir. The authors noted that the key difference between glargine and detemir was their pharmacokinetic profile and hence their posology – glargine was administered once daily and detemir either once or twice daily. With type 1 diabetics the median cost of prescriptions was 10% lower (p<0.001) amongst those treated with glargine than those treated with detemir. In two of the five components of the overall prescribing cost (sharps and hypoglycaemia rescue medication) the cost difference did not achieve statistical significance. Among type 2 diabetics the median cost of prescriptions was 28.1% lower amongst those treated with glargine compared with detemir (p<0.001). The largest single contribution to this was the difference in insulin cost, 31.7% lower in the glargine group (p<0.001). The median cost per year of oral antidiabetic medicine was slightly higher in the glargine group than the detemir group but this difference did not achieve statistical significance (p=0.096). Irrespective of treatment regimens the volume of insulin prescribed to patients with type 2 diabetes was consistently lower among those treated with glargine than detemir, whether standardized for basal exposure, or for both basal insulin exposure and patient's weight.

The Panel noted the authors' view that the results might have been influenced as detemir was only recommended in patients with type 2 diabetes as part of a basal-bolus regimen although clearly it could be used as a basal-oral anti-diabetic regimen. The authors also noted that further research needed to be undertaken to evaluate the long-term cost effectiveness of glargine over detemir. The Panel was concerned that this important caveat was not reflected in the material at issue. However the Panel did not consider the cost comparison misleading due to the more frequent use of the basal plus insulin regimen as alleged. No breach of the Code was ruled.

The Panel noted that there appeared to be a difference of views regarding the Levemir indication which according to Sanofi-Aventis had not changed. Currie *et al* (2007) which looked at similar data stated that in interpreting the evaluations there might be a familiarity effect with regard to glargine since it was launched earlier (2002 rather than 2004) and that the licence for detemir did not include management of type 2 diabetes except as part of a basal-bolus regimen. The Panel noted that the dates of first authorization in the SPCs were 9 June 2000 for Lantus and 1 June 2004 for Levemir. Poole *et al* stated that when the study was conducted from 2004 it was possible some physicians might have felt more comfortable prescribing glargine which had been available for a longer period than detemir and this might have influenced the results. Levemir could be used with oral anti-diabetics. The Panel queried whether the changes to Section 5.1 of the Levemir SPC would affect the prescription costs. However the Panel did not accept that the mailing was necessarily misleading if during the analysed period Levemir did not have a licence for the basal plus oral indication. At the time the mailing was sent Section 5.1 of the SPC referred to the use of Levemir with oral anti-diabetics. No breach of the Code was ruled.

Novo Nordisk was concerned that the claim 'Lantus significantly reduced hypoglycaemia over Levemir in

both type 1 and type 2 diabetes' highlighted that significant risk reduction was observed separately in type 1 and type 2 diabetes, whilst Currie *et al*'s analysis of hypoglycaemic events was conducted on the pooled patient cohort involving both types of diabetes. Since hypoglycaemic risk was clearly different in type 1 and type 2 diabetes, this claim was misleading. Further, the claim was substantiated with a retrospective cohort analysis, despite there being head-to-head randomized clinical trials both in type 1 and type 2 diabetes with very different results and conclusions. In fact hypoglycaemic risk (major and nocturnal hypoglycaemic events) was significantly lower in the case of Levemir when it was compared with Lantus as part of basal-bolus therapy in type 1 diabetes (Pieber *et al* 2007). In type 2 diabetes these insulin preparations did not differ from a safety perspective when they were compared as part of basal plus oral regimen (Rosenstock *et al* 2006). Novo Nordisk alleged that claim did not reflect all the available evidence and thus it was misleading in breach of the Code.

The Panel noted the heading at page 3 'Lantus significantly reduces hypoglycaemia over Levemir in both type 1 and type 2 diabetes' was referenced to Currie *et al* which examined as a secondary endpoint the relative risk of hypoglycaemia of Levemir and Lantus and changes in weight. Analysis was conducted on a pooled patient cohort of type 1 and type 2 diabetics. The heading did not make this sufficiently clear and was misleading in this regard. A breach of the Code was ruled.

The Panel noted that the first bullet point on page 3 explained that the data was derived from a retrospective database analysis of routine general practice of people with diabetes. The Panel noted that in Pieber *et al* cited by Novo Nordisk, the overall risk of hypoglycaemia was similar with no differences in confirmed hypoglycaemia. The Panel considered that it was sufficiently clear that the data derived from an observational study. Readers would be aware, in general terms of the differences between observational studies and randomized clinical trials. The Panel did not consider on the basis of the two studies cited by Novo Nordisk that the data presented from Currie *et al* was per se misleading as alleged. No breach of the Code was ruled.

Novo Nordisk noted that the claims 'Lantus and insulin detemir had a similar effect on weight in people with type [sic] diabetes' and 'In people with type 2 diabetes, effect on weight was comparable with Lantus and insulin detemir' appeared as bullet points on page 3 of the mailing. Both were referenced to Currie *et al*. The Levemir summary of product characteristics (SPC) stated that it caused significantly less weight gain in type 2 patients than other basal insulin preparations such as Lantus when used as part of basal plus oral regimen (Levemir had been licensed for this indication since March 2007). This claim was based on Rosenstock *et al* (2006). The claims disregarded evidence from a trial providing a higher level of evidence than a retrospective cohort analysis, not to mention the Levemir SPC. Furthermore the authors concluded that, '… detemir showed benefits in terms of weight gain whereby those patients who switched to detemir had on average no evidence of any weight gain in the period following switching treatment', clearly drawing attention to this potential benefit of Levemir. Therefore the claims highlighting the equivalence of the two preparations contradicted the original intention of the authors in breach of the Code. Novo Nordisk alleged that the mailing was unfair, ambiguous, seriously misleading information and disparaged Levemir.

The Panel noted that Section 5.1 of the Levemir SPC stated that studies in patients with type 2 diabetes treated with basal insulin in combination with oral anti-diabetic medicines glycaemic control (HbA1C) with Levemir was comparable to NPH insulin and Lantus and associated with less weight gain. The Panel considered that there was a difference between the products in relation to weight gain in type 2 diabetics. A table illustrated the change in body weight after treatment with insulin. A 52 week study demonstrated a weight gain of 2.3kg and 3.7kg respectively for Levemir once or twice daily – and 4kg gain for Lantus. The statistical significance of this difference was not given. Novo Nordisk stated that the SPC data for weight gain was based on Rosenstock *et al* which compared Levemir and Lantus. The abstract stated that bodyweight increased less with Levemir than with Lantus in completers (3kg vs 3.9kg, p= 0.012) and in the intention to treat analysis (2.7kg vs 3.5kg, p= 0.03).

The Panel considered that the claims regarding effect on weight were misleading as they did not reflect the Levemir SPC regarding weight gain in type 2 diabetics. A breach of the Code was ruled. Upon appeal by Sanofi-Aventis the Appeal Board considered that the claims at issue were misleading as they did not reflect the totality of the data regarding the weight gain typically seen with Lantus and Levemir. The Appeal Board upheld the Panel's ruling of a breach of the Code.

In Pieber *et al* the change in body weight after 26 weeks' treatment in type 1 diabetics was not statistically significantly different with Levemir and Lantus (0.52kg vs 0.96kg, p = 0.193).

The claims at issue were referenced to Currie et at wherein type 2 diabetics treated with detemir appeared to show almost no weight gain on average in the first 6 months of treatment whereas those treated with glargine gained 0.5kg on average. These differences did not achieve statistical significance (p = 0.78). The discussion section noted that Levemir showed benefits in terms of weight gain whereby those patients who switched to Levemir had on average no evidence of any weight gain. The Panel considered, however, that there was an important difference between stating that two products were comparable to stating that there was no statistically significant difference between them. On balance the Panel considered that the claims at issue were inconsistent with the authors' views in Currie *et al* as alleged. A breach of the Code was ruled.

Novo Nordisk Limited complained about a mailing (ref API 07/1039) for Lantus (insulin glargine) sent by Sanofi-Aventis to UK health professionals with an interest in diabetes in May 2007. Novo Nordisk produced a competitor product, Levemir (insulin detemir).

Novo Nordisk stated that it had failed to resolve matters with Sanofi-Aventis, and was reluctant to engage in conciliation as it considered that the mailer had already caused significant damage to the reputation of Levemir. Due to the nature of this one-off mailing Novo Nordisk considered that the only acceptable way to resolve this matter would be a corrective statement from Sanofi-Aventis. Sanofi-Aventis had ignored this request.

1 Claim 'Lantus offers a significant cost advantage over insulin detemir in both type 1 and type 2 diabetes'

This claim on page 2 of the mailing was followed by two bullet points which claimed that Lantus treatment costs were 10% lower and 28% lower ($p<0.001$) in type 1 and type 2 diabetes respectively, than for insulin detemir. All of the claims were referenced to a retrospective data analysis by Poole *et al* (2007).

COMPLAINT

Novo Nordisk alleged that the cost comparison was in breach of Clause 7.2 of the Code since Poole *et al* clearly emphasised that there was a significant difference between the two products in terms of the applied insulin regimens in type 2 diabetes. Poole *et al* thus did not compare like with like. The more frequent use of basal plus oral regimen with Lantus thus related to lower costs therefore the overall claim about the reduced treatment-related costs in type 2 diabetes was unfair and misleading. Furthermore during the analysed period Levemir did not have a licence for basal plus oral indication which meant that this economic evaluation also analyzed data from patients who used Levemir off-label. Whilst it was widely acceptable to report such data as part of an independent peer-reviewed scientific publication, using it for promotional purposes placed this issue at a different angle. The supplementary information to Clause 7.2 of the Code stated that an economic evaluation must be consistent with the marketing authorization, therefore using Poole *et al* for promotional claims was in breach of the Code.

RESPONSE

Sanofi-Aventis stated that the mailing reported on data from two peer-reviewed publications examining the effectiveness and prescribing costs of Lantus compared with Levemir in the treatment of type 2 diabetes. These studies were observational, retrospective, database analyses performed from one of the UK's largest general practice research databases (The Health Improvement Network (THIN) comprising records from over 5 million patients registered with a UK GP).

With regard to the allegation that the comparison on prescribing costs was unfair, inferring that Sanofi-Aventis had failed to comply with the supplementary information to Clause 7.2 that, 'valid comparisons can only be made where like is compared with like', Sanofi-Aventis understood that this requirement related to price comparisons, ie a comparison of the unit cost of individual medicines, not a comparison of the cost of treatment of conditions.

Sanofi-Aventis submitted that in applying the Code correctly, the requirement of such a cost comparison was that 'Care must be taken to ensure that economic evaluation … is borne out by the data available and does not exaggerate its significance'. The mailing undertook a robust assessment of the data available, the studies were performed according to protocols approved by an independent ethics committee and peer reviewed prior to publication. The size of the THIN database and the fact that it represented such a significant proportion of the UK population implied that the findings were appropriate to generalise to the UK as a whole, and were likely to accurately represent the true effectiveness and cost-effectiveness of the products when used in the UK. Therefore the significance of the results was relevant to the audience and was not exaggerated, in keeping with the requirements of the Code for such an economic comparison.

With regard to the concern that the two patient groups were not identical and that this implied that a fair comparison was not possible, Sanofi-Aventis submitted that the information reported simply captured the different use of the products in day-to-day clinical practice. Whilst in a randomised controlled trial (RCT) a demographic imbalance between patient groups would be a significant source of bias, a RCT would fail to detect differences due to unequal utilisation rates in normal practice. The great strength of a real life observational study was that any difference detected reflected the real usage pattern of the products, and this was essential if an accurate cost and cost-effectiveness analysis was to be performed - the economic case would only be valid if it fully took into account how the products were used in practice. This was particularly so in this case, where it might be relevant that the different rates of treatment with additional antidiabetic agents might be due to the differences in the effectiveness of the products. To suggest that such a comparison was unfair and misleading was misguided - by their very nature, effectiveness and cost-effectiveness needed to incorporate such differences at their core to properly understand how products were effective in clinical practice.

Novo Nordisk had suggested that a difference in the individual product licences in force for the period studied might account for different rates of use of concomitant oral antidiabetic agents between the two products, stating that the combination of Levemir and oral hypoglycaemic agents was not specifically indicated (off-label) during this time. However, the current marketing authorization for Levemir showed that the indication 'Treatment of diabetes mellitus',

was the same now as when the study was performed (Levemir summary of product characteristics (SPC) 1 June 2004) and this was comparable to that for Lantus ('For the treatment of adults, adolescents and children of 6 years or above with diabetes mellitus, where treatment with insulin is required'). Both these indications remained generalised to the treatment of diabetes, and neither precluded the concomitant use of oral antidiabetic agents during the period studied. Although the marketing authorization for Levemir had subsequently benefited from the addition to Section 5.1 of information about its use with oral antidiabetic agents, the 2004 SPC certainly did not preclude their concomitant use, which occurred in 27% of patients in this study. There was no such restriction stated in either the contraindications or warnings/precautions sections, and the section on drug interactions suggested that doses of concomitant oral agents might need to be reduced when used with Levemir, implying a common expectation of concomitant use of this class of medicine.

In summary, the evidence supporting the economic argument was appropriate, it being a robust, peer-reviewed analysis of the observed use of the products compared in the setting of everyday practice in the UK health environment and, contrary to the argument of Novo Nordisk, was consistent with not only the current marketing authorizations but also the marketing authorizations relevant to the period in which the data was collected. This complied with the Code and high standards had been maintained.

PANEL RULING

The Panel noted that the mailing was entitled 'Which basal insulin analogue has lower anti-diabetic prescribing costs compared with Levemir in similar patients?' Beneath 'Once-daily Lantus' it continued 'Evidence from a retrospective database analysis of routine general practice of people with diabetes being initiated on basal insulin therapy'. Page 2 was headed 'Lantus offers a significant cost advantage over Levemir in both type 1 and type 2 diabetes'.

Pages 1 and 2 were referenced to Poole *et al* which compared the costs of diabetes treatments, administration and monitoring following initiation of treatment with glargine or detemir regimens in type 1 or type 2 diabetes mellitus patients. The source data was a database of UK patients treated in general practice. The study showed that prescribing costs were significantly lower in patients treated with glargine than those treated with detemir. The study authors noted that the key difference between glargine and detemir was their pharmacokinetic profile and hence their posology – glargine was administered once daily and detemir either once or twice daily. With type 1 diabetics the median cost of prescriptions was 10% lower ($p<0.001$) amongst those treated with glargine than those treated with detemir. In two of the five components of the overall prescribing cost (sharps and hypoglycaemia rescue medication) the cost difference did not achieve statistical significance. Among type 2 diabetics the median cost of prescriptions was 28.1% lower amongst those treated with glargine compared with detemir ($p<0.001$). The largest single contribution to this was the difference in insulin cost, 31.7% lower in the glargine group ($p<0.001$). The median cost per year of oral antidiabetic medicine was slightly higher in the glargine group than the detemir group but this difference did not achieve statistical significance ($p=0.096$). Irrespective of treatment regimens the volume of insulin prescribed to patients with type 2 diabetes was consistently lower among those treated with glargine than detemir, whether standardized for basal exposure, or for both basal insulin exposure and patient's weight.

The Panel noted the authors' view that the results might have been influenced as detemir was only recommended in patients with type 2 diabetes as part of a basal-bolus regimen although clearly it could be used as a basal-oral anti-diabetic regimen. The authors also noted that further research needed to be undertaken to evaluate the long-term cost effectiveness of glargine over detemir. The Panel was concerned that this important caveat was not reflected in the material at issue. However the Panel did not consider the cost comparison misleading due to the more frequent use of the basal plus insulin regimen as alleged. No breach of Clause 7.2 was ruled.

The Panel noted that there appeared to be a difference of views regarding the Levemir indication which according to Sanofi-Aventis had not changed. Currie *et al* (2007) which looked at similar data stated that in interpreting the evaluations there might be a familiarity effect with regard to glargine since it was launched earlier (2002 rather than 2004) and that the licence for detemir did not include management of type 2 diabetes except as part of a basal-bolus regimen. The Panel noted that the dates of first authorization in the SPCs were 9 June 2000 for Lantus and 1 June 2004 for Levemir. Poole *et al* stated that when the study was conducted from 2004 it was possible some physicians might have felt more comfortable prescribing glargine which had been available for a longer period than detemir and this might have influenced the results. Levemir could be used with oral anti-diabetics. The Panel queried whether the changes to Section 5.1 of the Levemir SPC would affect the prescription costs. However the Panel did not accept that the mailing was necessarily misleading if during the analysed period Levemir did not have a licence for the basal plus oral indication. At the time the mailing was sent Section 5.1 of the SPC referred to the use of Levemir with oral anti-diabetics. No breach of Clause 7.2 was ruled on this point.

During its consideration of this matter the Panel considered that, from the claims at issue, prescribers would assume that the prescribing costs for all of their type 1 and all of their type 2 diabetics would be 10% and 28% lower if they prescribed Lantus instead of Levemir respectively. The Panel queried whether this was so based on median costs. The claims at issue did not refer to median costs. The Panel requested that the parties be advised of its concerns in this regard.

2 Claim 'Lantus significantly reduced hypoglycaemia over Levemir in both type 1 and type 2 diabetes'

This claim appeared as a bullet point on page 3 of the mailing referenced to Currie *et al*. This claim was followed by a bullet point which stated that in a retrospective data analysis of routine general practice of diabetics being initiated on basal insulin therapy showed that hypoglycaemia was reduced by 30% when they switched from other treatments to Lantus. The claim was referenced to Currie *et al* which, as with Poole *et al* above, used data from the THIN database.

COMPLAINT

Novo Nordisk had two major concerns.

Firstly the claim highlighted that significant risk reduction was observed separately in type 1 and type 2 diabetes, whilst in Currie *et al*, analysis on hypoglycaemic events was conducted on the pooled patient cohort involving both types of diabetes. Since hypoglycaemic risk was clearly different in type 1 and type 2 diabetes, this claim was misleading. Secondly, the claim was substantiated with a paper publishing a retrospective cohort analysis, despite there being head-to-head randomized clinical trials both in type 1 and type 2 diabetes with very different results and conclusions. In fact hypoglycaemic risk (major and nocturnal hypoglycaemic events) was significantly lower in the case of Levemir when it was compared with Lantus as part of basal-bolus therapy in type 1 diabetes (Pieber *et al* 2007). In type 2 diabetes these insulin preparations did not differ from a safety perspective when they were compared as part of basal plus oral regimen (Rosenstock *et al* 2006). Novo Nordisk alleged that claim did not reflect all the available evidence and thus it was misleading in breach of Clause 7.2 of the Code.

RESPONSE

Sanofi-Aventis submitted that the statement 'both type 1 and type 2' was intended to convey the concept of a pool of patients with both type 1 and type 2 diabetes, as opposed to a single cohort of patients with one of type 1 or type 2 disease.

Whilst Sanofi-Aventis agreed that if taken in isolation this headline might appear ambiguous, when placed in context with the rest of the data on the page the meaning became clear. The detailed text that explained the headline stated that the reductions in hypoglycaemia were observed in 'people with diabetes' - implying a pooling of patients with both types of the disease. Taking the page as a whole into consideration, the information presented was consistent with the published data - to omit to mention that the study contained patients with both type 1 and type 2 diabetes would be inappropriate, and the detailed text made it clear it was a pooled comparison of patients.

Sanofi-Aventis noted that Novo Nordisk had contested that the data observed in real life did not match exactly those seen in RCTs and suggested that this was therefore not a fair summary of all the information available (although only two RCTs were cited in making this argument). Whilst agreeing that RCT data were often fundamental to the evaluation of any new product or intervention, a range of data sources were collectively crucial in determining the impact of any given therapy in real life, including observational data. RCTs had their own limitations, in particular being performed on a highly selected cohort of patients which reduced the ability to generalise results to real life practice. A large observational study such as Currie *et al* was much more generalisable to the population than a small RCT and, contrary to Sanofi-Aventis's suggestion, a good quality observational study was rated level 2b in standard evidence based medicine hierarchies, the same level as a poor quality RCT.

Although individual RCT reporting was generally high quality, overall reporting of product-related trials was generally accepted to be susceptible to bias; Pieber *et al* cited by Novo Nordisk was a good example of this. The choice of evening-only administration of Lantus was questionable (the marketing authorization suggested dosing at any time of day) and had the effect of introducing a trial design that better favoured Levemir. Although Novo Nordisk highlighted the statistically significant differences in hypoglycaemia (higher in the Lantus group) it failed to mention the fact that the overall risk of hypoglycaemia was similar with no differences in confirmed hypoglycaemia. This inappropriate omission of the more significant comparison was in itself disingenuous.

In summary, the claims made from this observational study were a true representation of the effectiveness of the products in normal practice that had been demonstrated by appropriate scientific methodology, and as such significantly added to the evidence base available. The results were not inconsistent with the marketing authorizations and had been reported in a fashion that was consistent with the Code.

PANEL RULING

The Panel noted the heading at page 3 'Lantus significantly reduces hypoglycaemia over Levemir in both type 1 and type 2 diabetes' was referenced to Currie *et al* which examined as a secondary endpoint the relative risk of hypoglycaemia of Levemir and Lantus and changes in weight. Analysis was conducted on a pooled patient cohort of type 1 and type 2 diabetics. The heading did not make this sufficiently clear and was misleading in this regard. A breach of Clause 7.2 was ruled.

The Panel noted that the first bullet point on page 3 explained that the data was derived from a retrospective database analysis of routine general practice of people with diabetes. The Panel noted that in Pieber *et al* cited by Novo Nordisk, the overall risk of hypoglycaemia was similar with no differences in confirmed hypoglycaemia. The Panel considered that it was sufficiently clear that the data derived from an observational study. Readers would be aware, in general terms of the differences between observational studies and randomized clinical trials. The Panel did not consider on the basis of the two studies cited by

Novo Nordisk that the data presented from Currie *et al* was per se misleading as alleged. No breach of Clause 7.2 was ruled.

3 Claims 'Lantus and insulin detemir had a similar effect on weight in people with type [sic] diabetes' and 'In people with type 2 diabetes, effect on weight was comparable with Lantus and insulin detemir'

These claims appeared as bullet points on page 3 of the mailing. Both were referenced to Currie *et al*.

COMPLAINT

Novo Nordisk alleged that the claims at issue were in breach of Clause 7.2 of the Code. The Levemir summary of product characteristics (SPC) stated that it caused significantly less weight gain in type 2 patients than other basal insulin preparations such as Lantus when used as part of basal plus oral regimen (Levemir had been licensed for this indication since March 2007). This claim was based on Rosenstock *et al* (2006). The claims disregarded evidence from a trial providing a higher level of evidence than a retrospective cohort analysis, not to mention the Levemir SPC. Furthermore the authors (Currie *et al*), concluded that, '… detemir showed benefits in terms of weight gain whereby those patients who switched to detemir had on average no evidence of any weight gain in the period following switching treatment', clearly drawing attention to this potential benefit of Levemir. Therefore the claims highlighting the equivalence of the two preparations contradicted the original intention of the authors in breach of Clause 11.4 of the Code.

Novo Nordisk alleged that the mailing was in breach of Clause 7.2 in several aspects. It contained unfair, ambiguous, seriously misleading information and disparaged Levemir.

RESPONSE

Sanofi-Aventis noted that Novo Nordisk had stated that the SPC specifically stated that Levemir caused significantly less weight gain in type 2 patients than other basal insulin preparations. Sanofi-Aventis could find no such statement of significance in the SPC. Although the SPC stated that lower levels of weight gain were seen with Levemir, there was no attribution of significance (which was however specifically mentioned for several other comparisons), and the figures for weight gain in the SPC were different from those cited by Rosenstock *et al* that the Novo Nordisk provided to support its position. The claims in the mailing on weight gain were therefore not inconsistent with the marketing authorizations for either product.

Sanofi-Aventis agreed that Currie *et al* noted that 'patients who switched to Levemir had on average no evidence of weight gain'. The mailing did not contest this point - it simply reported the findings of the study which were that patients treated with Lantus had comparable levels of weight change to those treated with Levemir. (Interestingly, this was also reported by, Pieber *et al* 2007, where levels of weight change were not different between the two products). In total, the claims about weight gain met the requirements of the Code and high standards had been maintained.

In summary, the mailing was a fair representation of a well designed, well reported observational study that was widely generalisable to the UK population. This was not inconsistent with the marketing authorization for either product now (when the study was reported) or in 2004 (the time from which the data in the study was examined). The item complied with the Code and high standards had been maintained.

Finally, Sanofi-Aventis noted that Novo Nordisk had raised the issue that, inter-company discussions Sanofi-Aventis had failed to address the request that a corrective statement be sent to all those who received the original item. Having addressed all the concerns raised in the initial complaint, Sanofi-Aventis submitted its response made this moot. However, as Novo Nordisk had again raised this request, Sanofi-Aventis would of course issue such a statement if this item was ruled to be in breach of the Code to the degree that the Code of Practice Appeal Board considered this was appropriate, but recognised that it was the appropriate body to make this decision not Novo Nordisk.

PANEL RULING

Section 5.1 of the Levemir SPC stated that studies in patients with type 2 diabetes treated with basal insulin in combination with oral anti-diabetic medicines glycaemic control (HbA1C) with Levemir was comparable to NPH insulin and Lantus and associated with less weight gain. The Panel considered that there was a difference between the products in relation to weight gain in type 2 diabetics. A table illustrated the change in body weight after treatment with insulin. A 52 week study demonstrated a weight gain of 2.3kg and 3.7kg respectively for Levemir once or twice daily – and 4kg gain for Lantus. The statistical significance of this difference was not given. Novo Nordisk stated that the SPC data for weight gain was based on Rosenstock *et al* which compared Levemir and Lantus. The abstract stated that bodyweight increased less with Levemir than with Lantus in completers (3kg vs 3.9kg, p= 0.012) and in the intention to treat analysis (2.7kg vs 3.5kg, p= 0.03).

The Panel considered that the claims regarding effect on weight were misleading as they did not reflect the statement in the Levemir SPC regarding weight gain in type 2 diabetics. A breach of Clause 7.2 of the Code was ruled. This ruling was appealed.

In Pieber *et al* the change in body weight after 26 weeks treatment in type 1 diabetics was not statistically significantly different with Levemir and Lantus (0.52kg vs 0.96kg, p = 0.193).

The claims at issue were referenced to Currie et at wherein type 2 diabetics treated with detemir appeared to show almost no weight gain on average in the first 6 months of treatment whereas those treated with glargine gained 0.5kg on average. These

differences did not achieve statistical significance (p = 0.78). The discussion section noted that Levemir showed benefits in terms of weight gain whereby those patients who switched to Levemir had on average no evidence of any weight gain. The Panel considered, however, that there was an important difference between stating that two products were comparable to stating that there was no statistically significant difference between them. On balance the Panel considered that the claims at issue were inconsistent with the authors' views in Currie *et al* as alleged. A breach of Clause 11.4 was ruled. This ruling was not appealed.

APPEAL BY SANOFI-AVENTIS

Sanofi-Aventis noted that the mailing contained the claim that 'Lantus and insulin detemir had a similar effect on weight …' referenced to Currie *et al* that had demonstrated a minimal change in weight (1kg or less over 9 months) with no significant difference between the two products.

Sanofi-Aventis noted that the Panel considered this claim to be misleading as the data were contrary to a statement in the Levemir SPC. Although Sanofi-Aventis acknowledged that the Levemir SPC stated that the product was associated with less weight gain than Lantus, it did not consider that the claim had misrepresented or misled regarding the effect of Levemir on weight. The Levemir SPC indicated that the product caused weight gain to some degree and the promotional claim was consistent with this.

Sanofi-Aventis submitted that the new finding that it had reported was essentially that the weight change associated with Lantus was lower in this study than that previously recognised, and it was not unreasonable to draw attention to this new information concerning Lantus, not Levemir. Although this statement was no longer consistent with the Levemir SPC sentence 'associated with less weight gain', this was not due to a change in or suggestion that the existing knowledge of Levemir was incorrect - at no stage did this paper or the claim suggest that the change in weight associated with Levemir was any different from that recognised in the SPC.

In principle Sanofi-Aventis submitted that it was important to be able to present new data concerning a company's own products, and that it was unreasonable that dissemination of new data was restricted by mention of a product's properties in a competitor's SPC - a competitor company might not be motivated to update out-of-date information. It should also be considered that there might be instances of conflicting information between the SPCs of a product and the mention of the same in the SPC of another medicine. How could a claim be made that would always be contrary to one of the SPCs?

In summary, Sanofi-Aventis submitted that the claim that the level of weight gain seen with Lantus was lower than previously reported, and this was not inconsistent with the Lantus SPC. The claim did not challenge the concept that Levemir was also associated with weight gain, which was also consistent with the Levemir SPC. The only inconsistency with the claim was that the new data presented on Lantus meant that the Levemir SPC now contained out-of-date data on Lantus, and Sanofi-Aventis submitted that to be restricted by this was neither rational nor reasonable from a scientific and medical standpoint.

COMMENTS FROM NOVO NORDISK

Novo Nordisk noted that the claim that Lantus and Levemir had comparable effects on weight in type 2 diabetes was substantiated by Currie *et al* which reported results of a retrospective database analysis of proprietary data from The Health Improvement Network. The authors compared the outcomes of care in people with type 1 and type 2 diabetes following switching to treatment with either Lantus or Levemir in UK routine general practice. One of the secondary outcomes of this analysis was to compare weight changes after switching. The paper did not state anything about weight changes in type 1 diabetes but only showed a graph without making any conclusion. In terms of the findings from type 2 diabetes the paper also presented a graph and reported no weight gain in the first 6 months of treatment with Levemir and a 0.5kg average weight gain with Lantus; the difference was not statistically significant.

Novo Nordisk stated that it was aware that it was not the scope of its comment to criticise Currie *et al*, a scientific paper published by independent authors. Indeed Novo Nordisk had emphasised its concerns regarding the validity of the findings in an appropriate scientific way and sent a letter to the editor of the journal (Freemantle *et al*, 2007). However during the analysed time period there was a major difference between the parts of the SPCs which specified how Levemir and Lantus could be used in the treatment of diabetes mellitus. While Lantus could be used as a part of either basal+oral or basal-bolus regimens, Levemir could only be used as part of basal-bolus therapy, at that time. Although there was no data from this perspective in the paper, one had to assume that a considerably higher proportion of patients used a basal+oral regimen in the Lantus group than in the Levemir group since this regimen was the most popular way to start insulin therapy in type 2 diabetes. Therefore the authors did not compare 'like with like' in the case of type 2 diabetes. Novo Nordisk noted that despite finding a statistically, non-significant weight gain difference between the two products in type 2 diabetes, the authors had highlighted in the Discussion section that '…[Levemir] showed benefits in terms of weight gain whereby those patients who switched to [Levemir] had on average no evidence of any weight gain in the period following switching treatment'.

Novo Nordisk alleged that using only one reference to substantiate a promotional claim and disregarding all the other evidence showing exactly the opposite, as well as neglecting the relevant statement from the Levemir SPC, was cherry-picking the data.

In terms of other evidence Novo Nordisk first noted

the statement from the Levemir SPC that 'Studies in patients with type 2 diabetes treated with basal insulin in combination with oral antidiabetic drugs demonstrates that glycaemic control (HbA1c) with Levemir is comparable with NPH insulin and [Lantus] and associated with less weight gain, please see table 2 below.'

Table 2 set out the change in body weight after treatment with insulin determir, NPH insulin and insulin glargine at 20, 26 and 52 weeks.

Novo Nordisk stated that this was a clear statement, from the highest level of evidence, that Levemir had a weight benefit compared to Lantus in type 2 diabetes when insulin treatment was started. The statement was scientifically based on the results from a head-to-head comparison of the two preparations as part of basal+oral therapy in a randomized clinical trial (Rosenstock *et al*).

Furthermore Novo Nordisk noted that Levemir had been shown to cause less weight gain than Lantus when used as part of basal+bolus therapy in type 2 diabetes (Raskin *et al* 2006). In a randomized controlled clinical trial, a head-to-head comparison of the two compounds revealed a significant difference in terms of treatment-associated weight gain. While patients on Levemir therapy (+rapid-acting insulin analogue at mealtimes) gained an average 1.4kg during the 26 weeks of the trial, treatment with Lantus resulted in an average weight gain of 2.9kg (inter-group difference 1.48kg, p<0.0026).

Novo Nordisk noted that due to the limited amount of data from head-to-head comparisons between Levemir and Lantus, it also highlighted the weight results from randomized clinical trials when the two basal analogues were compared with NPH insulin. Firstly Novo Nordisk noted results from clinical trials where the basal insulin preparations were applied as part of basal+oral therapy.

Novo Nordisk had conducted two clinical trials in which Levemir was compared to NPH insulin in patients who were previously insulin-naïve (Hermansen *et al* 2006). The use of Levemir was associated with an average weight gain of 1.2kg during the 26-week long trial period, whilst NPH insulin caused an average weight gain of 2.8kg (difference 1.6kg, p<0.001). Further analysis of these results showed that the higher the patient's body mass index (BMI) at baseline, the smaller the weight gain he/she experienced.

Novo Nordisk noted that this association was also confirmed by Philis-Tsimikas *et al*, (2007), where the Levemir associated weight gain was 0.7kg whilst the weight gain in the NPH arm was 1.6kg (difference 0.9kg, p=0.005). This weight gain was observed in the trial arms where the insulin preparations were given in the evening, which was the traditional way to use the basal+oral combination (Philis-Tsimikas *et al* 2006)

Novo Nordisk noted that different results were seen in terms of the randomized clinical trials where Lantus was used as part of basal+oral therapy. Lantus was launched five years ago and Sanofi-Aventis had conducted several clinical trials, a summary of the weight results from these trials was provided.

	Weight change with) insulin glargine (kg)	**Weight change NPH insulin (kg)**	**p**
Fritsche *et al*, 2003	+3.7±3.6*	+2.9±4.3*	p=NS
Yki-Jarvinen *et al*, 2006	+2.6±0.6	+3.5±0.7	p=NS
Yki-Jarvinen *et al*, 2000	+2.57±0.23	+2.34±0.23	p=NS
HOE 901/2004 Study Investigators Group 2003	+0.31 (insulin glargine 30) +0.64 (insulin glargine 80)	+0.68	p-value was not published
Riddle *et al*, 2003	+3.0±0.2	+2.8±0.2	p=NS
Rosenstock et al, 2001**	+0.4	+1.4	p<0.0007

* in case of injecting the insulin preparations in the evening

** 62% of the patients on the Lantus arm used bolus insulin preparation as well, whilst in the NPH arm 64% of the subjects applied bolus insulin.

Novo Nordisk noted that it had conducted two randomized controlled trials in type 2 diabetes and focused on basal-bolus therapy, comparing Levemir with NPH insulin as the basal part of the regimen. In Haak *et al*, (2004), use of Levemir was associated with an average weight gain of 1kg whilst the NPH group gained an average of 1.8kg (p=0.017). Raslova *et al*, 2004, revealed an average weight gain of 0.51kg in the Levemir group vs 1.13kg in the NPH group (p=0.038). However in this latter trial the authors compared a full analogue basal-bolus regimen (insulin detemir + insulin aspart) with a full human insulin regimen (NPH insulin + human soluble insulin), therefore the difference in weight gain could not solely be attributed to the difference between the basal preparations. Regarding basal-bolus randomized clinical trials in type 2 diabetes with Lantus, the only one Novo Nordisk could identify was Rosenstock *et al*, (see table above) which studied a mixed group of previously insulin-naïve or insulin-treated patients with type 2 diabetes.

Novo Nordisk submitted that scientific theories, might explain why these basal insulin analogues had different impacts on patients' weight. There were two areas undergoing investigation, both theories explained the observed weight difference by the different mode of action of the two preparations. After injection into the human body the mode of action of Lantus was similar to that of NPH insulin, whilst Levemir acted in a different way. The molecule of Levemir was acylated with a free fatty acid chain through which it bound to albumin molecules in the body.

Novo Nordisk alleged that the first theory explained the weight benefit of Levemir with its relative hepato-selectivity compared to other exogenous insulin

preparations, such as Lantus. In normal physiology there was a portal-peripheral insulin gradient in the human body, since insulin was normally secreted into the portal vein system. In the case of exogenous insulin preparations this hepato-peripheral gradient was shifted towards the peripheral tissues causing relative hyperinsulinaemia in target organs (eg muscle, fat). Since the Lantus albumin complex could not penetrate through the endothelium in the peripheral tissues, but could penetrate the liver because of the fenestrated capillary wall in the sinusoids, the relative peripheral hyperinsulinaemia was shifted back to the portal system, which might decrease the peripheral lipogenesis in patients treated with Levemir. This relative hepato-selectivity was confirmed by a clamp trial involving healthy volunteers and comparing Levemir with NPH insulin (Hordern *et al*, 2005).

Novo Nordisk alleged that the other hypothesis explained the weight benefit with increased insulin signalling in the hypothalamus with Levemir compared to NPH insulin (Hennige *et al*, 2006). Since this part of the central nervous system played a crucial role in the control of satiety, this theory assumed that Levemier might have an enhanced effect on this part of the brain thus it might affect the satiety of patients in a favourable way.

Novo Nordisk alleged that on the basis of the above, the amount and perhaps more importantly the level of medical evidence suggesting a weight benefit of Levemir, when compared with Lantus and NPH insulin, was more than capable of substantiation. The medical evidence was further strengthened by the biological and pharmacological plausibility of the mechanisms underlying this consistent benefit of Levemir.

Therefore Novo Nordisk agreed that the claims at issue were misleading and were in breach Clause 7.2 of the Code. Further, Novo Nordisk also agreed with the Panel's ruling that the claims were inconsistent with the views of Currie *et al* and were in breach of Clause 11.4. In fact Novo Nordisk failed to understand how Sanofi-Aventis had appealed against the Panel's ruling of a breach of Clause 7.2 but not against the breach of Clause 11.4.

APPEAL BOARD RULING

The Appeal Board noted that the claims at issue 'Lantus and insulin detemir had a similar effect on weight in people with type [sic] diabetes' and 'In people with type 2 diabetes, effect on weight was comparable with Lantus and insulin detemir' were referenced to Currie *et al*, an observational study, wherein type 2 diabetics treated with Levemir appeared to show almost no weight gain on average in the first 6 months of treatment whereas those treated with Lantus gained 0.5kg on average. This difference did not achieve statistical significance ($p = 0.78$).

The Appeal Board noted however that a number of randomised clinical trials had shown that Levemir was associated with less weight gain than Lantus.

The Appeal Board considered that the claims at issue were misleading as they did not reflect the totality of the data regarding the weight gain typically seen with Lantus and Levemir. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. The appeal was unsuccessful.

Complaint received	**21 August 2007**
Case completed	**4 February 2008**

CASE AUTH/2045/9/07

LILLY v NOVO NORDISK

Promotion of Levemir

Lilly complained about an advertisement for Levemir (insulin detemir) issued by Novo Nordisk which was presented as an advertorial, entitled 'Levemir in type 2 diabetes an overview for primary care'. Under the subtitle 'Levemir-recent research and evidence' were the author's details. Prescribing information for Levemir was included. Lilly supplied a range of insulins.

The advertisement detailed four Novo Nordisk sponsored trials including PREDICTIVE (Lüddeke *et al*, 2006) which was a multinational, non-interventional, uncontrolled observational study designed to evaluate the incidence of serious adverse reactions, including major hypoglycaemic events, during Levemir treatment over 12, 26 or 52 weeks in type 1 or type 2 diabetics. The study involved 30,000 adults and children. The data included in the advertisement was a subanalysis of a defined cohort of European patients with type 2 diabetes, who were insulin naïve, initiated on Levemir and followed for 12 weeks (n=1,798).

The advertisement made a number of claims derived from the PREDICTIVE study. Lilly alleged that in the absence of an active comparator the claims that '… the initiation of Levemir is effective for patients with type 2 diabetes, without increasing the risk of hypoglycaemia' and 'the number of major hypoglycaemic events were significantly reduced for both daytime (p=0.021) and all (p=0.013)' could not be substantiated and were misleading. The second claim potentially compromised patient safety. The Levemir summary of product characteristics (SPC) stated 'Hypoglycaemia is a common undesirable effect. It may occur if the insulin dose is too high in relation to the insulin requirement. From clinical investigations it is known that major hypoglycaemia, defined as requirement for third party intervention, occurs in approximately 6% of patients treated with Levemir. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death'.

Hypoglycaemia was a significant and potential life-threatening side effect of insulin therapy and despite being listed in the Levemir SPC as common, nowhere in the advertisement had the risk with Levemir been highlighted and incidence data were not included. Lilly alleged that the advertisement was inconsistent with the Levemir SPC.

Lilly alleged that the claim 'Weight advantages with Levemir' was also at variance with the Levemir SPC which stated that 'Studies in patients with type 2 diabetes treated with basal insulin in combination with oral antidiabetic drugs demonstrates that glycaemic control (HbA1c) with Levemir is comparable to NPH insulin and insulin glargine and associated with less weight gain'. However, weight gain ranging from 0.7kg to 3.7kg was associated with Levemir treatment, varying with dosing and duration of treatment.

This was an uncontrolled observational study, and any findings in patients who had initiated Levemir would be confounded by a number of other factors including changes in other diabetes medicines and any lifestyle interventions which might be instituted as part of clinical practice. It was not possible to extrapolate from this data that any reported weight advantages were attributable to Levemir. Therefore the claim 'weight advantages with Levemir' was not capable of substantiation.

The advertisement stated that 52% of patients lost weight. This had been further detailed as: 43%, 26.3% and 15.6% of patients lost 1, 2 or 3kg respectively followed by the statement: 'Of those reviewed over half lost an average of more than 2.5kg in weight in only 12 weeks'. Lilly alleged it was very difficult to reconcile these ambiguous figures.

Lilly alleged that the undue emphasis placed on weight change within the advertisement, as evidenced by the large graph, was misleading. Weight change was not the primary objective of the study and indeed could be self-reported by patients, contributing to substantial bias. Therefore any claims of weight change derived from this study were misleading.

Lilly alleged that the advertisement was disguised promotion. It resembled an editorial written independently by a respected peer. Sponsorship of this advertisement had not been declared. It potentially misled health professionals and in particular might compromise patient safety. In Lilly's view this brought discredit to, and reduced confidence in, the pharmaceutical industry.

The Panel noted that the advertisement, presented in the style of an advertorial, was clearly headed 'Advertisement Feature'. The Panel considered that the layout and presentation of the advertisement was such that readers would not be misled as to its promotional nature. Prescribing information was included. The Panel thus did not consider that the advertisement was disguised promotion and so no breach was ruled. As it was clearly an advertisement no declaration of sponsorship was required. Prescribing information was clearly provided and so readers would know that the advertisement had been produced by Novo Nordisk. No breach of the Code was ruled.

The advertisement included a section describing the PREDICTIVE study. The claim 'This suggests that the initiation of Levemir is effective for patients with type 2 diabetes, without increasing the risk of hypoglycaemia' was not a stand alone claim; it came at the end of a block of text which discussed the 12 week data from a subgroup of the PREDICTIVE study. Previous text described the subgroup population ie type 2 diabetics who, at baseline were insulin-naïve and uncontrolled on oral anti-diabetic medicine. Adding Levemir to the existing oral therapy did not increase the risk of hypoglycaemia compared to baseline. In that regard the Panel considered that, given the context in which the claim appeared, it was clear that the comparison was with baseline ie oral antidiabetic therapy alone, and so in that regard the claim could be substantiated. The absence of an active comparator in this context did not mean that the claim could not be substantiated as alleged. No breach of the Code was ruled.

Similarly the claim 'The number of major hypoglycaemic events were significantly reduced for both daytime (p= 0.021) and all (p=0.013)' was not a stand alone claim but part of the text describing the PREDICTIVE study subgroup data. Lilly had not cited a clause and thus the Panel made no ruling on this point.

The Panel considered that prescribers would be well aware that insulin therapy was associated with a risk of hypoglycaemia. The advertisement at issue reported a reduced number of major hypoglycaemic episodes in type 2 diabetics before and after the addition of Levemir to their existing oral therapy. The advertisement did not state or imply that there was no risk of hypoglycaemia with Levemir therapy. In that regard, and given the audience to whom it was directed, the Panel did not consider that the advertisement was inconsistent with the particulars listed in the Levemir SPC. No breach of the Code was ruled.

The claim 'Weight advantages with Levemir' was a stand alone claim as it appeared as the heading to a section discussing the results from the PREDICTIVE study subgroup data for type 2 diabetics. The associated text referred to a mean decrease in weight of 0.6kg from baseline to week 12 in type 2 diabetics. It was further explained that during the study 52% of patients lost weight, 16% maintained the same weight and 32% had an increase in weight. A prominent bar chart depicted the results and in that regard emphasised the weight loss observed in the PREDICTIVE type 2 diabetes subgroup.

The Panel noted that the Levemir SPC stated that in studies in type 2 diabetes, patients treated with Levemir plus oral antidiabetic medicines gained less weight than those treated with Lantus plus oral antidiabetic medicines.

The Panel considered that with regard to changes to be expected in body weight, the advertisement was inconsistent with the Levemir SPC. In the Panel's view the advertisement implied that, in general, patients lost weight when Levemir was initiated whereas the SPC stated that they gained weight, albeit less than with other insulins. The Panel considered that although the advertisement reported the findings of the PREDICTIVE study, such findings were inconsistent with the particulars listed in the SPC. A breach of the Code was ruled. The Panel further considered that, in general, the claim 'Weight advantages with Levemir' was thus misleading and could not be substantiated. Breaches of the Code were ruled.

The Panel considered that the detailed weight data, as presented, was difficult to interpret as alleged. The percentages of patients losing 1,2 or 3kg were cumulative not absolute although this was not explained, thus it appeared that 15.6% of patients lost 3kg of weight, 26.3% lost 2kg of weight and 43% lost 1kg of weight which was not so. In that regard the Panel considered that the advertisement was misleading and ambiguous. A breach of Clause 7.2 of the Code was ruled. The Panel noted that Novo Nordisk had acknowledged that this part of the advertisement could have been written more clearly.

Upon appeal by Novo Nordisk of the Panel's rulings regarding weight the Appeal Board upheld the Panel's rulings of breaches of the Code.

Overall the Panel did not consider that either generally or in relation to the hypoglycaemic data that the advertisement warranted a ruling of a breach of Clause 2 of the Code.

Eli Lilly and Company Limited complained about a double page advertisement (ref UK/LM/0607/0040) for Levemir (insulin detemir) issued by Novo Nordisk Limited which appeared in Pulse, August 2007. The advertisement, which was presented as an advertorial, was entitled 'Levemir in type 2 diabetes an overview for primary care'. Under the subtitle 'Levemir-recent research and evidence' were the author's details. Prescribing information for Levemir appeared on the second page. Lilly supplied a range of insulins.

COMPLAINT

Lilly noted that it had set out its concerns about the advertisement in a letter to Novo Nordisk. Copies of the correspondence were provided. Lilly stated that it was clear that the two companies did not agree.

Lilly noted that Novo Nordisk had only responded to the comments made in respect of the risk of hypoglycaemia and the weight benefit of Levemir and not to comments that this advertisement did not declare sponsorship by Novo Nordisk and/or might be viewed as disguised promotion. Lilly noted Novo Nordisk's response 'In this article we have clearly specified that the weight change of -0.6kg was the mean for the whole subgroup …'. This was an explicit statement that the material was Novo Nordisk's and not Pulse's nor the author's. Lilly reiterated its concerns in respect of Clauses 9.10 and 10.1 of the Code, given this admission, together with the fact that the advertisement contained Levemir prescribing information and a Novo Nordisk promotional code.

Lilly's letter to Novo Nordisk stated that while the article had been authored by a GP, it had clearly been approved for promotional use by Novo Nordisk as evidenced by the inclusion of the prescribing information, promotional identifying code number and date of preparation. Indeed it appeared under the title 'Advertisement Feature'. Lilly alleged this advertisement was in breach of the Code on a number of grounds.

This article detailed four Novo Nordisk sponsored trials; the PREDICTIVE observational study (Lüddeke *et al*, 2006), a study comparing once-daily Levemir with NPH insulin (Philis-Tsimikas *et al*, 2006) and studies comparing insulin devices focusing on Novo Nordisk Flexpen (Lawton and Berg, 2001) and Innolet (Shelmet *et al*, 2003).

Lilly considered that data reported from the PREDICTIVE observational study was at variance with the Levemir summary of product characteristics (SPC).

PREDICTIVE was a multinational, non-interventional, uncontrolled observational study designed to evaluate the incidence of serious adverse reactions, including major hypoglycaemic events, during Levemir treatment over 12, 26 or 52 weeks in type 1 or type 2 diabetics. The study involved 30,000 adults and children. The data included in the advertisement was a subanalysis of a defined cohort of European patients with type 2 diabetes, who were insulin naïve, initiated on Levemir and followed for 12 weeks (n=1,798).

The advertisement made a number of claims derived from the PREDICTIVE study. Firstly, it was claimed that '… the initiation of Levemir is effective for patients with type 2 diabetes, without increasing the risk of hypoglycaemia'. Lilly alleged that in the absence of an active comparator such a conclusion could not be substantiated and was misleading in breach of Clause 7.4.

It was also claimed that 'the number of major hypoglycaemic events were significantly reduced for both daytime (p=0.021) and all (p=0.013)'. Again, in the absence of an active comparator, such a conclusion could not be substantiated and was misleading, potentially compromising patient safety. The Levemir SPC stated 'Hypoglycaemia is a common undesirable effect. It may occur if the insulin dose is too high in relation to the insulin requirement. From clinical investigations it is known that major hypoglycaemia, defined as requirement for third party intervention, occurs in approximately 6% of patients treated with Levemir. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death'.

Hypoglycaemia was a significant and potential life-threatening side effect of insulin therapy and despite being listed in the Levemir SPC as common, nowhere in the item had the risk with Levemir been highlighted to readers and incidence data were not included. Lilly alleged that the advertisement was thus not in accordance with the terms of the Levemir marketing authorization and was inconsistent with the particulars listed in the Levemir SPC in breach of Clause 3.2.

Secondly, it was claimed that there were 'Weight advantages with Levemir'. This claim was also at variance with the Levemir SPC which stated that 'Studies in patients with type 2 diabetes treated with basal insulin in combination with oral antidiabetic drugs demonstrates that glycaemic control (HbA1c) with Levemir is comparable to NPH insulin and insulin glargine and associated with less weight gain'. However, weight gain ranging from 0.7kg to 3.7kg was associated with Levemir treatment, varying with dosing and duration of treatment.

This was an uncontrolled observational study, and any findings in patients who had initiated Levemir would be confounded by a number of other factors including changes in other diabetes medicines and any lifestyle interventions which might be instituted as part of clinical practice. It was not possible to extrapolate from this data that any reported weight advantages were attributable to Levemir. Therefore the claim 'weight advantages with Levemir' was not capable of substantiation. Breaches of Clauses 7.2 and 7.4 were alleged.

Lilly submitted that the weight data, as presented, were very difficult to interpret. In the advertisement it had been stated that 52% of patients lost weight. This had been further detailed as follows: 43%, 26.3% and 15.6% of patients lost 1, 2 or 3kg respectively. This was followed by the statement: 'Of those reviewed over half lost an average of more than 2.5kg in weight in only 12 weeks'. Within this advertisement feature it was very difficult to reconcile these figures and in Lilly's view it was ambiguous in breach of Clause 7.2.

Lilly alleged that the undue emphasis placed on weight change within the advertisement, as evidenced by the large graph, was misleading. Weight change was not the primary objective of the study and indeed could be self-reported by patients, contributing to substantial bias. Therefore any claims of weight change derived from this study were misleading.

The advertisement was designed to resemble an editorial written independently by a respected peer. Sponsorship of this advertisement had not been declared, in breach of Clause 9.10. It was also Lilly's view that this represented disguised promotion, in breach of Clause 10.1 of the Code.

Pulse was the UK's leading medical weekly, counting 80% of GPs among its regular readers. Therefore, this misleading advertisement had been widely disseminated, disguised as a review by a respected peer. It potentially misled health professionals and in particular might compromise patient safety. In Lilly's view this brought discredit to, and reduced confidence in, the pharmaceutical industry (Clause 2).

Lilly asked Novo Nordisk to immediately stop using claims from the PREDICTIVE observational study without appropriate qualification, clearly detailing the limitations of the study design. All claims should be consistent with the SPC. In addition, Lilly asked Novo Nordisk, in an effort to redress that miscommunication, to issue a corrective statement of equal prominence in Pulse acknowledging the issues as set out above.

RESPONSE

Novo Nordisk noted that Lilly's primary concern related to the alleged lack of a declaration of sponsorship on the advertisement (Clause 9.10), and disguised promotion (Clause 10.1). Novo Nordisk believed that it was clear to the reader that the material was an advertisement for Levemir and two different Novo Nordisk insulin devices because: both pages were headed 'Advertisement Feature'; Levemir prescribing information had been included; adverse event reporting was requested to be made to Novo Nordisk and the two pages featured large pictures of Levemir-related insulin devices. Novo Nordisk did not see how someone could interpret this advertisement as an independent review. Pulse regularly featured advertorial pieces of this style and its readers would be sufficiently accustomed to their promotional nature. Novo Nordisk denied breaches of Clauses 9.10 and 10.1 of the Code.

The PREDICTIVE observational trial was a multinational, non-interventional, uncontrolled and observational study designed to evaluate the real-life safety and efficacy of Levemir in day-to-day clinical practice. Novo Nordisk's primary aim was to reveal any safety or efficacy concerns which would contradict the findings from its extensive randomized clinical trial programme; the PREDICTIVE data analyzed so far had confirmed the favourable results from the randomized clinical trials Novo Nordisk had conducted with Levemir (Dornhorst *et al*, 2007). Novo Nordisk would never promote any results from an uncontrolled observational trial which contradicted the existing data from trials of a higher level of evidence.

Risk of hypoglycaemia with insulin detemir

Lilly had alleged that the claim of '… the initiation of Levemir is effective for patients with type 2 diabetes, without increasing the risk of hypoglycaemia' could not be substantiated due to the lack of an active comparator in the trial.

The trial did have a comparator period which was precisely defined regarding hypoglycaemic events. Patients were asked to report the number of hypoglycaemic events during the four weeks preceding the initiation of Levemir (baseline visit). The hypoglycaemic event rate during the period was compared to the rate during the last four weeks of the observation period, before the final visit. One could argue about potential recall bias, however Novo Nordisk believed that every patient who had had a major hypoglycaemic event (requiring third party intervention) in the recent past would be able to recall it. Since major hypoglycaemic events had a significant risk reduction when compared to the risk with previous treatment, Novo Nordisk believed that this claim could be substantiated with the results from this subgroup of PREDICTIVE. Lilly also emphasized its concern regarding the contradiction between these data and a statement from the Levemir SPC. Novo Nordisk noted that the major hypoglycaemic event rate in the SPC was primarily derived from randomized clinical trials conducted in type 1 diabetes. In these trials Levemir was used as part of basal-bolus therapy. Since type 1 diabetes was related to much higher rates of hypoglycaemic events, it was difficult to interpret this statement to an insulin-naïve subgroup of type 2 diabetics using basal+oral therapies.

Furthermore, Novo Nordisk provided data on major hypoglycaemic event rates (24 hour) from its randomized clinical trials conducted in insulin-naïve type 2 diabetics after initiation of Levemir. These trials compared the hypoglycaemic risk of Levemir with the hypoglycaemic risk of NPH or Lantus. Baseline characteristics of patients in these trials were comparable with those in the subgroup of PREDICTIVE.

- Comparison of once-daily Levemir with NPH insulin added to a regimen of oral antidiabetic medicines in poorly controlled type 2 diabetes (Philis-Tsimikas *et al*)
  - o Major hypoglycaemic events with Levemir injected in the evening: 2 events/20 weeks (0.03 event/patient year)
  - o Major hypoglycaemic events with Levemir injected in the morning: 0 events/20 weeks
  - o Major hypoglycaemic events with NPH insulin injected in the evening: 0 events/20 weeks.

- A 26-week, randomized, parallel, treat-to-target trial compared Levemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naïve type 2 diabetics (Hermansen *et al*, 2006)
  - o Major hypoglycaemic events with Levemir: 1 event/21 weeks (0.01 event/patient year)
  - o Major hypoglycaemic events with NPH insulin: 8 event/24 weeks (0.08 event/patient year)

- Levemir vs Lantus as add-on to current oral antidiabetic therapy in insulin-naïve type 2 diabetics (Rosenstock *et al*, 2006)
  - o Major hypoglycaemic events with Levemir: 9 events/52 weeks (0.03 event/patient year)
  - o Major hypoglycaemic events with Lantus 8 events/52 weeks (0.03 event/patient year).

The major hypoglycaemic event analysis of the PREDICTIVE subgroup revealed a patient/year event rate of less than 0.01, which seemed to be better than findings from the randomized clinical trials.

The significant risk reduction Novo Nordisk observed during the observational period (compared to the baseline event rate with previous oral antidiabetic therapy alone) could not be compared with any data from its randomized clinical trial due to the lack of hypoglycaemic data before randomization in the above studies. However, there were reliable data on major hypoglycaemic event rates with oral antidiabetic therapy in type 2 diabetes. This rate was typically between 0.009 and 0.028 event/patient year (Leese *et al*, 2003, Shorr *et al*, 1997) which might explain the significant risk reduction of major hypoglycaemic events in PREDICTIVE. Furthermore a recently published comprehensive review about hypoglycaemia in type 2 diabetes (Zammitt and Frier, 2005) also referred to the authors' own experience with basal+oral regimen and reported no major hypoglycaemic events following insulin initiation.

With regard to all hypoglycaemic event rates observed in Novo Nordisk's trial, it agreed with the potential criticism that the rate was underestimated due to recall bias. However such recall bias would also be relevant in the case of recalling the prestudy event rate (with oral antidiabetic therapy alone). Therefore this kind of bias did not have any impact on the interpretation of the results comparing the two periods. On this basis, Novo Nordisk believed the claim could be substantiated from the PREDICTIVE study and confirmed the findings of the major hypoglycaemic event rates revealed in its clinical trials referred to above. Therefore Novo Nordisk could not accept the argument that these hypoglycaemia results would not be valid and rejected Lilly's allegations that health professionals had been misled and patient safety compromised.

In the recently published European Association for the Study of Diabetes/American Diabetes Association (EASD/ADA) guideline for the management of hyperglycaemia in type 2 diabetes, the authors highlighted that in different treat-to-target clinical trials the observed frequencies of severe hypoglycaemic episodes in type 2 diabetes were between 1 and 3 events/100 patient-years (Nathan *et al*, 2006). This rate was comparable with the frequency detected in the PREDICTIVE study (0.01 event/patient-year). Novo Nordisk submitted that health professionals knew that there was a risk of hypoglycaemia in any case of insulin treatment. This advertisement did not conflict with such practical experience, but provided reliable data on the frequency of major hypoglycaemic events to be expected after insulin initiation with Levemir.

Novo Nordisk noted that the advertisement contained results not only from its PREDICTIVE observational trial, but also from a randomised clinical trial in a comparable patient population. The findings on major hypoglycaemic events from this trial (Philis-Tsimikas *et al*) were very similar to the findings in the PREDICTIVE study. Lilly repeatedly referred to that part of the Levemir SPC which stated that the average frequency of major hypoglycaemic events was 6%. Novo Nordisk noted that this event rate came from randomized clinical trials conducted in type 1 diabetes, when Levemir was used as part of basal-bolus therapy. Since it was beyond any question that type 1 diabetes related to a much higher frequency of hypoglycaemic events, omitting such differences between basal-bolus and basal+oral therapies (Diabetes Control and Complications Trial Research Group, 1993), rendered the comparison between the hypoglycaemic event rate from the PREDICTIVE study (the subject of this piece) and the rate from the SPC incongruous. Therefore Novo Nordisk did not believe that the content of the advertisement about major hypoglycaemic events would mislead the relevant patient population or compromised patient safety.

Weight benefit of Levemir

Novo Nordisk strongly agreed that weight findings from an uncontrolled observational trial should be interpreted with caution if they contradicted findings from clinical trials of a higher level of evidence. However, this weight benefit was a consistent finding in all Novo Nordisk randomized clinical trails when Levemir was compared with other basal insulins regardless of the type of diabetes or the applied insulin regimen (Russell-Jones *et al*, 2004, Pieber *et al*, 2005, Home *et al*, 2004, Hermansen *et al*, 2004, Raslova *et al*, 2004, Haak *et al*, 2005, Robertson *et al*, 2007, Philis-Tsimikas *et al*, Hermansen *et al*, 2006, and Rosenstock *et al*). The only exception was a trial that compared Levemir with Lantus in type 1 diabetes as part of basal bolus therapy where the average weight gains were 0.52kg (Levemir) and 0.96kg (Lantus) with no statistically significant difference between the two (Pieber *et al*, 2007). In the following trials patients randomized to Levemir experienced:

- less average weight gain than patients with the comparator (Home *et al*,– $Idet_{morn+bed}$, Raslova *et al*, Haak *et al*, Philis-Tsimikas *et al*, Hermansen *et al*, 2006, Rosenstock *et al*) or
- weight neutrality (Home *et al*, – $Idet_{12\text{-}hour}$, Pieber *et al*, 2005 – $Idet_{morn+bed}$) or, an
- average weight loss when compared with patients on the comparator arm (Russell-Jones *et al*, Pieber *et al*, 2005 – $Idet_{morn+din}$, Hermansen *et al*, 2004).

Since insulin initiation in type 2 diabetes had been related to weight gain Novo Nordisk believed this finding from the PREDICTIVE trial should be shared with its customers. In the PREDICTIVE trial the weight benefit was revealed not only in this subgroup of type 2 diabetics, but also in type 2 patients switched from premix insulin preparations to Levemir and in users of a basal bolus regimen (both in type 1 and 2) when they were switched to Levemir from either NPH insulin or Lantus. Novo Nordisk did not know of any other insulin which could provide such consistent weight findings as Levemir.

Novo Nordisk believed it was difficult to interpret this weight benefit from all the above mentioned clinical trials other than to a phenomenon linked to the use of Levemir. There could be confounders in an observational trial which made it harder to interpret the results. However Novo Nordisk did not know of any potential confounder that would affect patients' weight consistently and favourably, regardless of the type of diabetes and the type of applied insulin regimen.

Lilly had specified weight data from the Levemir SPC (0.7kg and 3.7kg). Novo Nordisk noted that this was from two different randomized clinical trials using a different number of basal insulin injections, over different trial periods. The PREDICTIVE subgroup analysed in this advertisement were those patients who were uncontrolled on oral antidiabetic therapy alone prior to PREDICTIVE and who entered PREDICTIVE on once daily Levemir and were followed for 12 weeks. This subgroup of patients mirrored those in Philis-Tsimikas *et al* except in this clinical trial oral antidiabetic therapy remained unchanged from randomization. This was why a table showing the change of oral antidiabetic therapy was included which Novo Nordisk was sure was one of Lilly's concerns regarding the weight changes in PREDICTIVE.

In the advertisement Novo Nordisk had clearly specified that the weight loss of 0.6kg was the mean for the whole

subgroup and highlighted the percentages of patients who gained weight (32%), remained the same weight (16%) and lost weight (52%) on average. Therefore Novo Nordisk rejected the allegation that the information on weight changes observed in this subgroup of patients from the PREDICTIVE trial could not be substantiated and potentially misled health professionals.

Novo Nordisk submitted that nothing in the advertisement suggested that Levemir had a weight sparing effect. Apart from providing the weight findings for the readers, the summary clearly stated no more than 'heavier patients experienced a greater weight loss' during the observational period. This had also been reported in Novo Nordisk's randomized clinical trials (Hermansen *et al*, 2006). Furthermore, it would be seen from the article that data from PREDICTIVE was balanced with data from a randomized clinical trial (Philis-Tsimikas *et al*).

Although Novo Nordisk agreed that the detailed weight data giving the percentages of patients losing 1, 2 or 3kg of weight during the observational period could have been written more clearly, it did not mislead. The figures relating to the categories of average weight loss represented cumulative percentages. Despite not being straightforward, this information could be interpreted with common sense. It was difficult to make any other interpretation than this, since the paragraph above clearly stated the proportion of patients who lost, remained the same or gained weight during the study.

Novo Nordisk believed that the rising incidence of obesity, and hence type 2 diabetes, was one of the major challenges faced in healthcare. Thus every kind of antidiabetes medicine, having proven favourable effect on weight or preventing further weight gain when compared to other existing therapeutic modalities, should be communicated to the relevant health professionals.

Findings from the PREDICTIVE study had been shared with Novo Nordisk's customers so far in three different publications in peer-reviewed scientific journals (Meneghini *et al*, 2007, Lüdekke *et al* and Dornhorst *et al*). Since the launch of the trial, different aspects of the results had been presented 44 times at highly credible international scientific meetings and reflected the quality of data from PREDICTIVE. Low quality data would not have been so widely accepted.

Therefore Novo Nordisk had a clear intention to share the important findings of one of the largest observational trials ever conducted in diabetes, with health professionals. Any promotional piece containing information from the PREDICTIVE study also provided sufficient information for the readers to decide how the results should be interpreted. Novo Nordisk did not consider that it needed to emphasise the weaknesses of observational trials in general (given the fact that at least a short description of the trial was included in all of its materials). Novo Nordisk believed health professionals had the necessary epidemiological knowledge to allow them to make their own conclusions.

PANEL RULING

The Panel noted that the advertisement had appeared in Pulse. Although the material was presented in the style of an advertorial the Panel did not consider that it resembled normal editorial material in Pulse. It was clearly headed 'Advertisement Feature'. The highlighting in the advertisement was all in green whereas highlighted text in Pulse was always in shades of blue. The Panel considered that the layout and presentation of the advertisement was such that readers would not be misled as to its promotional nature. Prescribing information was included. The Panel thus did not consider that the advertisement was disguised promotion and so no breach of Clause 10.1 was ruled. As the piece was clearly an advertisement no declaration of sponsorship was required. Prescribing information was clearly provided and so readers would know that the advertisement had been produced by Novo Nordisk. No breach of Clause 9.10 was ruled.

The Panel noted that the advertisement included a section describing the PREDICTIVE study. The claim 'This suggests that the initiation of Levemir is effective for patients with type 2 diabetes, without increasing the risk of hypoglycaemia' was not a stand alone claim; it came at the end of a block of text which discussed the 12 week data from a subgroup of the PREDICTIVE study (Novo Nordisk data on file). Previous text described the subgroup patient population ie type 2 diabetics who, at baseline were insulin-naïve and uncontrolled on oral anti-diabetic medicine. The data on file showed that adding Levemir to the existing oral therapy did not increase the risk of hypoglycaemia compared to baseline. In that regard the Panel considered that, given the context in which the claim appeared, it was clear that the comparison was with baseline ie oral antidiabetic therapy alone, and so in that regard the claim could be substantiated. The absence of an active comparator in this context did not mean that the claim could not be substantiated as alleged. No breach of Clause 7.4 was ruled.

Similarly the claim 'The number of major hypoglycaemic events were significantly reduced for both daytime ($p=0.021$) and all ($p=0.013$)' was not a stand alone claim but part of the text describing the PREDICTIVE study subgroup data. However the Panel noted that Lilly had not cited a clause as required by Paragraph 5.2 of the Constitution and Procedure and thus made no ruling on this point.

The Panel considered that prescribers would be well aware that insulin therapy was associated with a risk of hypoglycaemia. The advertisement at issue examined the incidence of major hypoglycaemic episodes in type 2 diabetics before and after the addition of Levemir to their existing oral therapy and reported a reduced number. The advertisement did not state or imply that there was no risk of hypoglycaemia with Levemir therapy. In that regard, and given the audience to whom it was directed, the Panel did not consider that the advertisement was inconsistent with the particulars listed in the Levemir SPC. No breach of Clause 3.2 was ruled.

The claim 'Weight advantages with Levemir' was a

stand alone claim as it appeared as the heading to a section of text discussing the results from the PREDICTIVE study subgroup data for type 2 diabetics. The associated text referred to a mean decrease in weight of 0.6kg from baseline to week 12 in type 2 diabetics. It was further explained that during the study 52% of patients lost weight, 16% maintained the same weight and 32% had an increase in weight. A prominent bar chart depicted the results and in that regard emphasised the weight loss observed in the PREDICTIVE type 2 diabetes subgroup.

The Panel noted that the Levemir SPC stated that in studies in type 2 diabetes, patients treated with Levemir plus oral antidiabetic medicines gained less weight than those treated with Lantus plus oral antidiabetic medicines.

The Panel considered that with regard to changes to be expected in body weight, the advertisement was inconsistent with the Levemir SPC. In the Panel's view the advertisement implied that, in general, patients lost weight when Levemir was initiated whereas the SPC stated that they gained weight, albeit less than with other insulins. The Panel considered that although the advertisement reported the findings of the PREDICTIVE study, such findings were inconsistent with the particulars listed in the SPC. A breach of Clause 3.2 was ruled. The Panel further considered that, in general, the claim 'Weight advantages with Levemir' was thus misleading and could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled. These rulings were appealed.

The Panel considered that the detailed weight data, as presented, was difficult to interpret as alleged. The percentages of patients losing 1,2 or 3kg were cumulative not absolute although this was not explained, thus it appeared that 15.6% of patients lost 3kg of weight, 26.3% lost 2kg of weight and 43% lost 1kg of weight which was not so. In that regard the Panel considered that the advertisement was misleading and ambiguous. A breach of Clause 7.2 of the Code was ruled. The Panel noted that Novo Nordisk had acknowledged that this part of the advertisement could have been written more clearly.

Overall the Panel did not consider either generally or in relation to the hypoglycaemic data, that the advertisement warranted a ruling of a breach of Clause 2 of the Code which was reserved as a sign of particular censure. No breach of Clause 2 was thus ruled in relation to each matter.

APPEAL BY NOVO NORDISK

Novo Nordisk submitted that in terms of the inconsistency with the Levemir SPC, it noted that the regulatory authorities considered all the then available evidence when they granted permission to use Levemir in combination with oral antidiabetics. When Novo Nordisk submitted all the available evidence in October 2006 to the European Medicines Agency (EMEA), only a fraction of the results from the PREDICTIVE trial were available and there was no full peer-reviewed publication from the study. Therefore, there was no opportunity to provide them with the robust and convincing results from the largest observational study ever conducted in the field of insulin treatment in diabetes mellitus. During the last twelve months four clinical papers (Dornhorst *et al*, Ludekke *et al*, Meneghini *et al*, 2007/May, and Meneghini *et al*, 2007/November) were published in peer-reviewed journals; three of which analysed weight as a secondary outcome of the study (the fourth publication analysed baseline patient characteristics and predictors of hypoglycaemic events).

1 In Dornhorst *et al*, data of 20,531 patients with type 1 or type 2 diabetes were analysed. Weight decreased from baseline significantly by -0.1kg ($p<0.01$) and -0.4kg ($p<0.0001$) in type 1 and type 2 diabetes, respectively.

2 In insulin-naïve patients with type 2 diabetes (n=1321) from the German cohort of the PREDICTIVE trial analysed in Menghini *et al*, May, an average weight loss of -0.9kg was detected ($p<0.0001$). A similar weight reduction was found in patients who were switched to Levemir±OADs from NPH±OADs (-0.9kg, $p<0.0001$, n=251) or Lantus±OADs (-0.8kg, $p<0.0001$, n=260).

3 In the most recent publication Meneghini *et al*, November, which compared two different Levemir titration approaches in a randomized way, +1.1kg weight gain was observed in one arm of the trial whilst in the other arm +0.4kg weight gain was revealed (statistical comparison was made to detect any difference in the weight change between the two arms ($p=0.0314$)). These weight changes were found in the subcohort of patients with type 2 diabetes who were insulin-naïve at baseline.

Furthermore, Novo Nordisk noted that investigators of PREDICTIVE communicated the results in 28 oral or poster presentations on international diabetes meetings (IDF 2006, Cape Town, South-Africa; ADA 2007 Chicago and EASD 2007 Amsterdam). Novo Nordisk highlighted the weight findings from some published abstracts from these meetings:

IDF 2006

1 Aczel *et al* (abstract 119): weight reduction of 0.2kg was found both in type 1 (n=2426) and in type 2 (n=1610) diabetes ($p<0.001$ and $p<0.01$, respectively).

2 Ludekke *et al* (abstract 380): in n=6364 patients with type 1 diabetes an average weight reduction of 0.2kg ($p<0.001$) was observed whilst in type 2 diabetes (n=11901) a reduction of 0.5kg ($p<0.001$) was revealed.

3 King *et al* (abstract 921): in 306 patients with type 2 diabetes who were switched from either NPH or Lantus plus OADs to Lantus plus OADs, a weight reduction of 0.5 kg ($p<0.05$) was observed.

4 Sreenan *et al* (abstract 388): data of n=1583 patients with type 1 diabetes and n=743 patients with type 2 diabetes were analysed. These patients were treated with a basal-bolus insulin regimen. The basal part (Lantus) of the regimen was switched to Levemir at baseline. Investigators observed a weight reduction of 0.4kg and 0.5kg in type 1 and type 2 diabetes, respectively ($p<0.001$ in both cases).

5 Dornhorst *et al* (abstract 370): investigators found an average weight reduction of 0.7kg in 2314 patients with insulin-naïve type 2 diabetes when Levemir was introduced as initial insulin therapy (p<0.001).

ADA 2007

6 Sreenan *et al* (abstract 549-P): the weight change was analyzed in different subgroups of insulin-naïve patients with type 2 diabetes after Levemir initiation. When Levemir was combined with metformin+sulfonylurea (n=269) they observed a weight reduction of 0.4kg (p=NS). When sulfonylurea was discontinued and Levemir was used in combination with metformin (n=161) the weight reduction was 1.7kg (p<0.0001). In terms of combination of Levemir with thiazolodendione (TZD) (n=95), a weight gain of 0.3kg was found (p=NS), whilst in case of discontinuation of TZD (n=202) a weight reduction of 0.8kg was revealed (p<0.0115).

7 Gallwitz *et al* (abstract 550-P): patients initiated with once-daily Levemir in the morning (n=351) or evening (n=1,693) were compared in this analysis. In patients who injected Levemir in the morning, a non-significant weight loss of 0.3kg was observed, whilst those patients with an evening injection showed a significant weight reduction of 0.7kg (p<0.0001).

8 Dornhorst *et al* (abstract 2196-PO): investigators analysed weight change after initiation with Levemir or switching from another insulin to Levemir in 748 elderly patients (age≥65yrs) with type 2 diabetes. In patients who were insulin-naïve at baseline a weight reduction of 0.3kg was observed (p=NS), whilst in patients who were switched to Levemir from another insulin preparation a weight loss of 0.5kg was found (p<0.0001).

Novo Nordisk submitted that instead of making this comprehensive list of presentations from the PREDICTIVE trial even longer (Novo Nordisk provided a detailed list of the abstracts), it noted why it believed that these findings should be shared with health professionals. Inevitably, being overweight or obese were major public health problems which led to the development of several metabolic disorders such as insulin resistance and type 2 diabetes. They were not only risk factors which played important roles in the development of glucose intolerance but also co-morbidities which had major impact on the success of treating hyperglycaemia. In fact the recently published ADA/EASD treatment guideline emphasised that 'promoting weight loss or at least avoiding weight gain should remain an underlying theme throughout the management of type 2 diabetes, even after medications are used' (Nathan *et al*, 2006).

Novo Nordisk submitted that the above mentioned publications and abstracts from the PREDICTIVE trial further confirmed the important and consistent findings from the randomized clinical trials that Levemir had a weight advantage when compared to other basal insulin preparations. Bearing in mind that the PREDICTIVE results were not available when the EMEA made the last modification to the Levemir SPC, important findings from this large (>30,000 patients with diabetes), multinational (>20 countries), observational study should be shared with health professionals. It was generally acknowledged that observational studies might provide important and clinically relevant information which could not be fully revealed by smaller sized randomized clinical trials. Results from observational studies might be equally or even more relevant for clinical practice since they came from clinical practise itself. No one would deny that findings from an observational study should be handled carefully due to potential confounding factors. However, it remained that the weight advantage of Levemir as shown in the PREDICTIVE study was observed in patients with type 1 and type 2 diabetes, regardless of whether they were insulin-naïve or not. One potential confounding factor could, of course, be structured lifestyle education at the time of insulin initiation. However, such a consistent finding would not be a consequence of such education. The only one consistent therapeutic step in PREDICTIVE was to introduce Levemir, not an educational programme. Undoubtedly, the method of education, its intensity and content would be different in different countries and in different patient groups.

Novo Nordisk submitted that it had never promoted Levemir as a weight reducing medicine. This would, of course, be totally unacceptable in the case of any insulin preparation. Novo Nordisk was well aware of the difference of promoting an anti-obesity medicine and an insulin preparation that had shown a weight benefit. There was a huge difference in sharing the latest findings from a robust observational study or promoting it as a weight sparing medicine. This was precisely why the findings from PREDICTIVE were reported alongside those of a randomised clinical trial, in the advertisement.

In regard to the claim of 'Weight advantages with Levemir', Novo Nordisk submitted that claiming a 'weight advantage' had not meant the same as stating that the use of a product would result in weight loss. From all the evidence available a feature of Levemir, possibly due to its different mode of action, had an impact on weight gain that was not shown with other basal insulin preparations. This was the message that Novo Nordisk was endeavouring to communicate with this claim. Clearly, it was an advantage to use insulin that was associated with significantly less weight gain (type 2 insulin initiation) or no weight gain (type 1, basal bolus regimen), compared to other available basal insulin preparations, that were not associated with the same advantage.

Novo Nordisk submitted that weight management was an integral part of diabetes therapy, therefore finding such an advantage of an insulin preparation was an important one, which should be shared with health professionals. However, sharing this observation from an uncontrolled observational study (even if it was the largest ever conducted study in the field of insulin treatment and diabetes) would not be appropriate without providing the evidence along side randomized controlled trials. That was why the advertisement covered the findings from the PREDICTIVE trial and also from an important randomized clinical trial (Philis-Tsimikas *et al*, 2006) in order to provide 'accurate, balanced, fair, objective and unambiguous information' which was relevant for primary care physicians when

they started insulin treatment in type 2 diabetes. The two page advertisement clearly demonstrated this.

Novo Nordisk submitted that one interesting result relating to the weight change during the course of this randomized clinical trial was a trend for those people with the highest body mass index (BMI) at baseline to gain less weight compared to those with smaller BMI measures (Philis-Tsimikas *et al*, 2007).

Novo Nordisk submitted that the similar trend of weight change, with increasing baseline BMI, was also found in the subgroup analysis reported in the advertisement. At the time of the advertisement, the above analysis was not available otherwise it would have also been included. For these reasons, Novo Nordisk did not agree with the ruling of the Panel that the advertisement breached Clauses 7.2 and 7.4 of the Code.

COMMENTS FROM LILLY

Lilly noted that the promotion of a medicine must be in accordance with the terms of its marketing authorisation. In order for the PREDICTIVE data to be included in the SPC, a variation needed to be submitted to the European regulatory authorities for approval. This approval was not reflected in the current Levemir SPC. Lilly alleged that within the advertisement, weight 'advantages' with Levemir were reported as weight loss for 52% of patients, with 32% gaining weight. A prominent bar chart emphasised the weight loss observed in the study. Therefore, Novo Nordisk's claim that there were 'Weight advantages with Levemir' was at variance with the Levemir SPC which stated that 'Studies in patients with type 2 diabetes treated with basal insulin in combination with oral antidiabetic drugs demonstrates that glycaemic control (HbA1c) with Levemir is comparable to NPH insulin and Lantus and associated with less weight gain'. However, weight gain ranging from 0.7kg to 3.7kg was associated with Levemir treatment, varying with dosing and duration of treatment. Therefore, Lilly agreed with the Panel's ruling of a breach of Clause 3.2 in this regard.

Breach of Clauses 7.2 and 7.4

Lilly noted that PREDICTIVE was a multinational, non-interventional, uncontrolled observational study designed to evaluate the incidence of serious adverse drug reactions, including major hypoglycaemic events, during Levemir treatment over 12, 26 or 52 weeks in patients with both type 1 and type 2 diabetes. Lilly alleged that as this was an uncontrolled observational study, any findings in patients who had initiated Levemir were likely to be confounded by a number of other factors. These might include changes in other diabetes medications and any lifestyle interventions instituted as part of clinical practice. It was therefore not possible to extrapolate from this data that any reported weight 'advantages' were solely attributable to Levemir.

Lilly alleged that the advertisement implied that in general, patients lost weight with Levemir. It was not possible to extrapolate from this data that any reported weight advantages were attributable to Levemir. Therefore the claim 'Weight advantages with Levemir' could not be substantiated. In order to comply with the Code as laid out in Clauses 7.2 and 7.4 'Information, claims and comparisons must be accurate, balanced, fair, objective and unambiguous and must be based on up-to-date evaluation of all the evidence and reflect the evidence clearly. They must not mislead either directly or by implication, by distortion, exaggeration or undue emphasis. Materials must be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine' and 'Any information, claim or comparison must be capable of substantiation'. The weight data, as presented, were very difficult to interpret. In the advertisement feature it had been stated that 52% of patients lost weight. Further percentage of patients losing 1, 2 or 3kg was 43%, 26.3%, and respectively 15.6%. Lilly alleged that these results were cumulative, not absolute. In general, the claim 'Weight advantages with Levemir' was misleading and ambiguous and incapable of substantiation. Lilly therefore agreed with the Panel's ruling of a breach of Clauses 7.2 and 7.4.

Lilly submitted that the undue emphasis placed on weight loss within the advertisement, as evidenced by the large graph, was misleading. Weight loss was not the primary objective of the study and indeed weight could be self-reported by patients in the study, contributing to substantial bias. Therefore any claims of weight loss derived from this study were misleading to Novo Nordisk had stated that weight advantage had not meant the same as weight loss. While this might be correct, the data used to support this claim suggested that there would generally be weight loss associated with Levemir therapy. This was clearly at variance with the Levemir SPC and was misleading. Novo Nordisk also stated that weight management was an integral part of diabetes therapy. It was for this reason that it was impossible to extrapolate the suggested benefits of weight loss from this study design. The lack of a comparator within this study made any claims of weight advantage incapable of substantiation. Novo Nordisk also stated that it had never promoted Levemir as a weight loss medicine. However a recent advertisement highlighting that 'Levemir is changing figures' had recently been ruled in breach of the Code as being misleading, suggesting that Levemir treatment would result in weight loss. This decision was upheld on appeal.

Whilst Lilly supported the use of large observational studies to support the important primary endpoint of safety, the use of these studies to make other promotional claims should be done with caution and should be aligned with the SPC.

APPEAL BOARD RULING

The Appeal Board noted that the PREDICTIVE study was a prospective, observational, uncontrolled study designed to assess the safety and efficacy of Levemir in routine clinical practice in type 1 and type 2 diabetes. The claim 'Weight advantages with Levemir' appeared as the heading to a section of text discussing the results from the subgroup of insulin-naïve type 2 diabetics, uncontrolled on oral therapy (n=1,798). The associated text referred to a mean decrease in weight of 0.6kg from baseline to week 12. It was further explained that during the study 52% of patients lost weight, 16% maintained

the same weight and 32% had an increase in weight. A prominent bar chart depicted the mean weight change by BMI in type 2 diabetics initiated on Levemir. The advertisement also stated that 'of those patients reviewed (n=1,525) over half lost an average of more than 2.5kg in weight in only 12 weeks'. The Appeal Board did not consider that this was consistent with the figures provided for the percentage of patients losing 1kg (43%), 2kg (26.3%) or 3kg (15.6%) as ruled upon separately by the Panel.

The Appeal Board noted that the Levemir SPC stated that in studies in type 2 diabetes, patients treated with Levemir plus oral antidiabetic medicines gained less weight than those treated with Lantus plus oral antidiabetic medicines. The Appeal Board noted that the studies cited in the SPC were of 20 – 52 weeks' duration.

The Appeal Board noted a number of confounding factors in the PREDICTIVE study. In particular the use of sulphonylureas and glitazones, both of which were associated with weight gain, had decreased by the end of the study thus the observed weight loss might not have been entirely attributable to Levemir. It was further noted that weight could be self-reported by patients which in the Appeal Board's view might bias results towards weight loss rather than weight gain. In addition some patients, as a result of being observed, might have introduced lifestyle changes which might have had a beneficial effect on weight.

The Appeal Board considered that with regard to changes to be expected in body weight, the advertisement was inconsistent with the Levemir SPC and had not presented the balance of the evidence. In the Appeal Board's view the advertisement implied that, in general, patients lost weight when Levemir was initiated whereas the SPC stated that they gained weight, albeit less than with other insulins. The Appeal Board considered that although the advertisement reported their findings of the PREDICTIVE study, such findings were inconsistent with the particulars listed in the SPC. The Appeal Board upheld the Panel's ruling of a breach of Clause 3.2. The appeal on this point was unsuccessful. The Appeal Board further considered that, given the points discussed above the claim 'Weight advantages with Levemir' was thus misleading and could not be substantiated. The Appeal Board upheld the Panel's ruling of breaches of Clauses 7.2 and 7.4. The appeal on this point was unsuccessful.

Complaint received	**12 September 2007**
Case completed	**5 February 2008**

CASE AUTH/2046/9/07 *NO BREACH OF THE CODE*

TAKEDA v GLAXOSMITHKLINE

Press release on global corporate website

Takeda alleged that a press release placed on GlaxoSmithKline's global corporate website on 30 July which was headed 'GlaxoSmithKline presents Avandia data to [Food and Drugs Administration] FDA' was in breach of the Code including Clause 2. It was dated 30 July, bore the address for GlaxoSmithKline US and summarised the data regarding Avandia and increased risk of cardiovascular ischaemic events. The data was presented to an advisory committee of the FDA on 30 July 2007. The press release stated that GlaxoSmithKline believed that a full and scientific evaluation of all the data did not confirm the safety questions originally raised. The press release included important safety information about Avandia which referred to the FDA and company contact details for the UK and US media.

Takeda was concerned that the press release was placed on both the global website (www.gsk.com) as well as the US website (www.usa.gsk.com). The global website was however specifically directed towards a UK audience as evidenced by the following: the website was registered in the UK with US citizens being directed to a US website; there was no mention of any UK-specific website on the home page; for career opportunities in the UK one was directed to the global website; a Google search for GSK.co.uk directed one to www.gsk.com and the London Stock Exchange Share Price was given on the home page.

The press release was clearly directed towards a UK audience as at the end of it there were three London contact telephone numbers.

Thus GlaxoSmithKline in the UK was responsible and accountable for any information placed on the global website by the US affiliate.

Takeda did not accept GlaxoSmithKline's submission that the press release related to 'financial information' as there was no mention of any financial information. During inter-company dialogue the GlaxoSmithKline website was amended such that the information was 'labelled' as information for business journalists and analysts/investors. Takeda did not accept this and believed that all material in press releases should be in line with the Code and the spirit of the Code.

The Panel noted that the press release had been placed on the corporate website by GlaxoSmithKline US. It had been sent to UK financial media. The press release covered the FDA Advisory Committee which had occurred in the US and related to the US regulatory authorities. The data would obviously be of interest worldwide. The important safety information provided at the end of the press release related to the use of Avandia in the US.
The Panel noted that there had originally been two closely similar versions of the press release on the website. That accessed via 'Avandia News' did not originally feature a heading stating the intended audience. This was remedied by GlaxoSmithKline during inter-company dialogue.

GlaxoSmithKline was a UK headquartered company. It was not unreasonable for UK corporate contact details for the UK media to be included on the press release. The press release was issued in the UK to business/financial journalists, investors and analysts only. The issue would be relevant to such an audience.

The Panel noted that information or promotional material about prescription only medicines which was placed on the Internet outside the UK would be regarded as coming within the scope of the Code if it was placed there by a UK company or at the instigation or with the authority of such a company and if it made specific reference to the availability or use of the medicine in the UK.

The Panel considered that information about a prescription only medicine had been placed on the Internet by a UK company or an affiliate or at the instigation or with the authority of such a company. The Panel noted that the press release at issue referred to Avandia which was available in the UK. It included general information about Avandia but did not specifically refer to its availability or use in the UK. On the contrary the inclusion of important safety information related to the use of the product in the US. The press release related to a particular meeting of the FDA Advisory Committee and was issued as a corporate press release. The Panel did not consider that the press release came within the scope of the Code as alleged. The other allegations made by Takeda were as a consequence ruled not to be in breach of the Code, including of Clause 2.

Takeda UK Limited complained about a press release concerning Avandia (rosiglitazone) placed on the GlaxoSmithKline global corporate website on 30 July. Takeda supplied Actos (pioglitazone).

The press release was headed 'GlaxoSmithKline presents Avandia data to [Food and Drugs Administration] FDA'. It was dated 30 July and was issued on paper bearing the address for GlaxoSmithKline US. It summarised the Avandia scientific evidence available to address the question of increased risk of cardiovascular ischaemic events. The

data was presented to an advisory committee of the FDA on 30 July 2007. The press release stated that GlaxoSmithKline believed that a full and scientific evaluation of all the data did not confirm the safety questions originally raised. The press release included important safety information about Avandia which referred to the FDA and contact details for the UK media and the US media.

COMPLAINT

Takeda alleged that the press release was in breach of the Code. In addition, as the press release was placed on the Internet with global (which by definition also included European) access, it could also be considered to be in breach of the European Federation of Pharmaceutical Industries and Associations (EFPIA) Code of Practice on the Promotion of Medicines, as some of the statements and claims made within it were not in line with the Avandia summary of product characteristics (SPC).

'Avandia is the most widely studied oral anti-diabetic medicine for the treatment of Type 2 diabetes. The extensive data base for Avandia includes…'

The press release referred to an 'extensive data base' which included 116 clinical trials in over 52,000 patients. Of the 116 clinical trials mentioned, 113 were neither named nor referenced. For the three that were, Takeda noted that DREAM was conducted in patients who had raised blood glucose levels but were not medically classified as having type 2 diabetes, (and so not in accordance with the Avandia SPC), ADOPT was conducted in newly diagnosed type 2 diabetics who were drug naïve (so again, not in accordance with the Avandia SPC) and RECORD, which was described in the press release as 'specifically studying cardiovascular effects' only had an interim analysis currently available, so no final conclusions could be drawn from it. Similarly, the 'Study in a high risk cardiovascular-risk population: PPAR' was conducted in patients with metabolic syndrome (so once again not in accordance with the Avandia SPC).

Takeda alleged that the lack of referencing and the inclusion of studies outside the licence for Avandia which as monotherapy was indicated for type 2 diabetics who were inadequately controlled by diet and exercise, and for whom metformin was inappropriate because of contraindication or intolerance, rendered any claims with respect to 'The extensive database…' in breach of Clauses 3.2, 7.2, 7.3, 7.4, 7.6 and 7.9.

'Across the extensive dataset for Avandia, there is no consistent or systematic evidence that Avandia increases the risk of heart attack or cardiovascular death in comparison with other antidiabetic medicines'

Takeda alleged that this claim was not consistent with the Avandia SPC which mentioned under section 4.8 Undesirable effects, cardiac ischaemia as being a common side effect for rosiglitazone monotherapy, rosiglitazone in combination with metformin, rosiglitazone with sulphonyurea, and rosiglitazone with metformin and a sulphonyurea. Further there was also a statement that 'In a retrospective analysis of data from pooled clinical studies, the overall incidence of events typically associated with cardiac ischaemia was higher for rosiglitazone containing regimens 1.99% versus comparators, 1.51%'.

In the discussion at the FDA Advisory Committee on the 30 July 2007, the Committee after reviewing all the data from the FDA as well as that provided by GlaxoSmithKline voted 20:3 that in its opinion rosiglitazone was associated with an increase of myocardial ischaemia and infarction compared to placebo. Importantly, the press release made no mention of any comparison between rosiglitazone with placebo, and only referred to 'antidiabetic medicines', which as noted above was false, misleading and did not reflect all the available evidence. Breaches of Clauses 7.2 and 7.3 were alleged.

Consequently the above claim regarding cardiovascular safety was inconsistent with the SPC, was not accurate, balanced, fair, objective, was misleading, not capable of substantiation, did not give references, did not reflect all the evidence available regarding side effects and did not encourage the rational use of Avandia in breach of Clauses 3.2, 7.2, 7.3, 7.4, 7.9 and 7.10. In addition Takeda alleged that the claim was in breach of Clause 2.

Following the above claim, specific mention was made of cardiovascular events with which Takeda also had concerns.

'Myocardial ischaemia: There was no statistically significant increase in myocardial ischaemia in ADOPT, GlaxoSmithKline's long term comparator study.'

This was just one study, yet the extensive database referred to above contained 116 clinical trials for which no mention was made. The claim in any case relating to myocardial ischaemia, was contrary to the information given in section 4.8 of the SPC (as referred to above). The ADOPT study was conducted in newly diagnosed type 2 diabetics who were treatment naïve and so not in accordance with the Avandia SPC. In addition, ADOPT was neither specifically designed nor powered to evaluate myocardial ischaemia nor indeed any other cardiovascular outcome. Breaches of Clauses 3.2, 7.2, 7.3, 7.4, 7.9 and 7.10 were alleged.

'Heart attack: the number of heart attacks across the sources of data is small, the data are inconsistent, and the totality of the evidence does not show a difference between Avandia and the most commonly prescribed anti-diabetic agents. In three epidemiological database studies, the risk of heart attack was similar for Avandia compared to the other anti-diabetic agents, and in one database study comparing Avandia to Actos there was no difference.'

The comparison between Avandia and Actos was incorrect because in the documents provided by the

FDA, and indeed in GlaxoSmithKline's own submission to the FDA, Takeda noted that there was a study which showed that Actos was associated with a lower risk of heart attack compared to Avandia. Takeda alleged that the claim was false, misleading and disparaged other medicines in breach of Clauses 7.2, 7.3, 7.4, 7.6 and 8.1.

'CV death:the long-term trials provide no evidence of increased CV death or all cause mortality with Avandia compared to the most commonly prescribed oral antidiabetics.'

This was in contrast to the findings and conclusions in the New England Journal of Medicine meta-analysis which included 42 studies with a duration of more than 24 weeks. In this peer-reviewed journal the authors stated in the results section that 'in the rosiglitazone group as compared with the control group, the odds ratio for death from cardiovascular causes was 1.64 (95%Cl 0.92 to 2.74; P= 0.06) and that this achieved borderline significance'. So although GlaxoSmithKline might state that there was no increase in CV death, it did not reflect the conclusions of health professionals working in the field of diabetes, and the claim did not refer to rosiglitazone's increased risk of cardiac ischaemia compared with placebo as referred to in the SPC. Breaches of Clauses 3.2, 7.2, 7.3 and 7.4 were alleged.

'Stroke: Across the data sources, fewer strokes are observed with Avandia than with other anti-diabetic medicines, although the differences in the long-term trials were not statistically significant.'

Takeda did not know of any rosiglitazone studies where the incidence of stroke had been evaluated as a primary endpoint. Claims regarding the beneficial effects of Avandia in this respect therefore could not be made especially when it would seem according to the press release that the differences in long-term trials were 'not statistically significant'. This was inaccurate, false and misleading. Breaches of Clauses 3.2, 7.2, 7.3 and 7.4 were alleged.

'GlaxoSmithKline continues to support Avandia as safe and effective when used appropriately'.

The Code cautioned the use of the word 'safe' and stated that it must not be used without qualification (Clause 7.9). Describing Avandia as 'safe' was a claim that could not be made in the context of an FDA Advisory Committee meeting which was arranged specifically to look at its cardiovascular safety and where most (20:3) of the committee voted that rosiglitazone was associated with an increased risk of cardiac ischaemia. Furthermore as the information in this press release was so misleading, inaccurate and biased, Takeda questioned whether it would be possible for healthcare providers or patients who read it to use Avandia 'appropriately' based on the information given, which did not encourage the rational use of a medicine. Breaches of Clauses 2, 7.9 and 7.10 were alleged.

The last part of the press release contained:

'Important Safety Information for Avandia …'

Takeda stated that this section was specifically directed towards patients and was not in line with either the UK or the European patient information leaflet (PIL) for Avandia. In particular Takeda noted that it did not list all the possible side effects as given in section 4 of the PIL. At the very least it should list the thirteen 'very common side effects' from the PIL, and more specifically the 'very common cardiovascular side effects' which included 'chest pain resulting from reduced blood supply to the heart muscle' as well as a 'small increase in total cholesterol levels' and 'increased levels of fats in the blood'.

Breaches of Clauses 3.2, 7.2, 7.9 and 7.10 were alleged. Takeda further alleged that as this section was directed towards patients then it was also in breach of Clause 2.

Finally as this piece clearly promoted Avandia to patients in the UK and Europe, it was in breach of Clauses 20.1 and 20.2 not least as it was misleading with respect to the safety of the product.

Takeda was concerned that the press release was placed on both the global website (www.gsk.com) as well as the US website (www.usa.gsk.com). The global website was however specifically directed towards a UK audience as evidenced by the following: the website was registered in the UK with US citizens being directed to a US website; there was no mention of any UK-specific website on the home page; for career opportunities in the UK in GlaxoSmithKline one was directed to the global website; a Google search for GSK.co.uk directed one to www.gsk.com and the London Stock Exchange Share Price was given on the home page.

Regarding the press release itself, clearly the announcement was directed towards a UK audience as at the end of it there were three London telephone numbers given for the UK media to contact for further information.

Clause 21.2 stated that 'Information or promotional material about medicines covered by Clause 21.1 above which is placed on the Internet outside the UK will be regarded as coming within the scope of the Code if it was placed there by a UK company or an affiliate of the UK company. Thus GlaxoSmithKline in the UK was responsible and accountable for any information placed on the global website by the US affiliate.

Finally Takeda noted the following case precedents: Case AUTH/1937/1/07 where no breach was ruled as it was made quite clear that the information provided on the website was not directed towards a UK audience and Case AUTH/1527/10/03 where the Panel stated that 'If such material had been placed on the website by an affiliate of a UK company it could nonetheless, be caught by Clause 21.2 and thus come within the scope of the Code.'

Takeda did not accept GlaxoSmithKline's argument that the press release related to 'financial information' but as there was no mention of any financial

information at all. During inter-company dialogue the GlaxoSmithKline website was amended such that the information was 'labelled' as information for business journalists and analysts/investors. Takeda did not accept this and believed that all material in press releases should comply with the letter and spirit of the Code.

RESPONSE

GlaxoSmithKline strongly disagreed that this press release breached the ABPI Code or the EFPIA Code. The press release was entitled 'GlaxoSmithKline presents Avandia data to FDA' and was a true, fair and balanced summary, to the business and financial media, of the company's presentation to an FDA Advisory Committee meeting on Avandia in the US and was clearly stated as such. The presentation was publicly available on the FDA's website. GlaxoSmithKline provided two versions of this reference; one was what was seen on the computer screen while the other was what was printed when a hard copy was requested using standard print function. The difference between these two was that GlaxoSmithKline's logo and disclaimer did not appear on the latter.

Background

GlaxoSmithKline was committed to patient safety and the full transparency of its scientific information which was publicly available on the Clinical Trials Register (CTR) on the GlaxoSmithKline corporate website.

In 2006, as part of ongoing safety surveillance, GlaxoSmithKline pro-actively conducted a meta-analysis to investigate whether rosiglitazone might be associated with myocardial ischaemia. A very broad definition of myocardial ischaemia that included events such as shortness of breath and chest pain was used and the results suggested an increased risk of myocardial ischaemia. In order to further test this hypothesis GlaxoSmithKline conducted a large observational study in which the risk associated with rosiglitazone was similar to other antidiabetic agents. These data were submitted to the appropriate regulatory authorities and were reflected in the European SPC since October 2006.

Nissen and Wolski (2007) accessed GlaxoSmithKline's CTR database and conducted a meta-analysis of some of the data. The paper, published in the New England Journal of Medicine, generated an enormous amount of media interest, including the financial media. This was followed by editorials and other publications which continued to generate intense media interest. The intense media interest brought forward a planned review of rosiglitazone by the FDA, as the data was conflicting and inconsistent. This became a spotlight for lay, healthcare and financial media.

Meta-analysis was only one method used to assess the clinical data and the results were subject to significant confounding, particularly in this case when glycaemic endpoint studies were used to test a cardiovascular hypothesis, utilising predominantly adverse event reports. GlaxoSmithKline conducted a range of other studies and analyses to answer questions raised from the meta-analyses. As the results of these studies were significantly at odds with the meta-analysis data, their publication was considered of material importance with respect to the GlaxoSmithKline share price.

The press release was focused on rosiglitazone and was an accurate summary of the data presented to the FDA Advisory Committee meeting.

Over 50% of GlaxoSmithKline's investor base was in the UK market, and so there was a considerable investor and press following of the company. The company communicated with investors/press through a variety of means, including dissemination of press releases and stock exchange announcements.

If an announcement was deemed 'material' it would be issued via the London and New York stock exchanges. If it was not deemed 'material' but was deemed newsworthy (as in this case) a press release would be issued. Press releases were issued to subscribed lists of journalists/investors and analysts.

Whilst there were no formal disclosure obligations surrounding a press release, best practice ensured that company followers (investors, analysts and journalists) could access the information. Newswire reporting helped GlaxoSmithKline to disseminate information widely, but this was editorialised. To ensure that GlaxoSmithKline's position, in full, was available it published the press releases on the corporate website.

The issues surrounding Avandia had been material to the company, as evidenced by the fall in market value and share price reaction since the publication of the Nissen and Wolski analysis in May. At the time of this press release, the shares had fallen 17% with a resultant loss of approximately £12bn in market capitalisation.

Given this background, the FDA Advisory Committee meeting was critical, not least as there was a vote to remove the product from the market. Beforehand, and on the day of the meeting, there was significant interest from investors and journalists on the content and possible outcomes of the meeting, including specifically what GlaxoSmithKline would present.

The Advisory Committee meeting was clearly newsworthy for the company and of business relevance. Therefore a press release was issued to business journalists to provide them with a summary of information that was to be presented by the company at the meeting. The resulting vote from the meeting was issued as a stock exchange announcement later the same day.

In the UK, GlaxoSmithKline confirmed that the press release was issued to business/financial journalists, investors and analysts only. The GlaxoSmithKline 'UK' media contacts identified on the press release were responsible for managing communication with primarily business/financial journalists.

The press release was placed on the GlaxoSmithKline corporate website by the US arm of the company, on 30

July 2007 after 13.36hrs UK time (in advance of the Advisory Committee meeting), to ensure that company followers (investors, analysts and financial journalists) were able to access the information. This ensured that GlaxoSmithKline's position, in full, was available. The events covered in the press release occurred in the US and were specific to the US regulatory authorities. The press release was prefixed with Philadelphia and used the GlaxoSmithKline ticker on the New York Stock Exchange. The corporate website, www.gsk.com, had the following statement: 'GlaxoSmithKline is quoted on the London and New York stock exchanges. The company's shares are listed on the New York Stock Exchange in the form of American Depositary Shares (ADSs) and these are evidenced by American Depositary Receipts (ADRs), each one of which represents two ordinary shares.'

The intended audience was financial and business media – this was stated across the top of the press release when accessed from the Media Centre, and as noted by Takeda, during inter-company dialogue, GlaxoSmithKline UK requested its corporate colleagues to further clarify the header of the press release when accessed via 'Avandia News' in the news section of www.gsk.com, in an attempt to resolve this matter at an inter-company level. The header read 'The information on this page is intended for **business journalists and analysts/investors** [emphasis added]. Avandia is in the news because of an article in the New England Journal of Medicine about cardiovascular risk' and UK medical and consumer media were not directed towards the press release by e-alerts or otherwise. UK health professionals were not alerted to it. UK healthcare and lay media were the responsibility of GlaxoSmithKline UK which took no part in the dissemination or posting of this corporate release. No UK medical or consumer media journalist received the press release either proactively or reactively

As mentioned above, there were two ways to access the press release on the GlaxoSmithKline corporate website, via the 'Media Centre' or via 'Avandia News'. The Media Centre front page and the press release (when viewed from this route) had an alert at the top stating 'These press releases are intended for business journalists and analysts/ investors. Please note that these releases may not have been issued in every market in which GlaxoSmithKline operates'. The Avandia News version did not have this alert, but the wording cited above was added during inter-company dialogue to further clarify the intended audience for the press release when accessed via the Avandia News page.

GlaxoSmithKline submitted that a press release clearly intended for business and financial media was not promotional and as such was not subject to the promotional aspects of the Code. It was fair and balanced and therefore fulfilled the requirements of the Code regarding company press releases and ethical requirements. GlaxoSmithKline reiterated that this press release had never been used promotionally.

The website to which the press release was posted was the GlaxoSmithKline global corporate website, which contained information about worldwide events. The press release was clearly intended for the media and was therefore allowable under Clause 20.2. This was in common with Takeda's own practice on its global website www.takeda.com. As such, this was not a promotional item and did not contain claims. The GlaxoSmithKline corporate site also complied with Clause 21. The press release was not promotional and so Clause 20.2 was relevant in this instance. Whilst the press release was examined by GlaxoSmithKline UK (as required by the Code in compliance with the supplementary information to Clauses 20.2 and 14.3), as GlaxoSmithKline was a UK headquartered legal entity, it did not specifically refer to the availability or use of the medicine in the UK and therefore was not considered to come within the scope of the Code.

GlaxoSmithKline noted that the supplementary information to Clause 20.2 stated that business releases should identify the business importance of the information. Given the high profile nature of the discussions of the Avandia cardiovascular discussions in the lay and business press and its effect on the GlaxoSmithKline share price, it believed the business importance was self evident.

This was clearly a corporate press release referring to events in the US. These events were in the public domain and the data mentioned in the press release was presented to the US regulatory body. As the press release reported on data presented to the US regulatory body, it was appropriate that it was based on the US licence which formed the reference point for this important news item; in that regard Takeda's reference to the European SPC was erroneous.

GlaxoSmithKline disagreed with the allegation that the press release did not comply with the EFPIA Code. The EFPIA Code did not cover non-promotional, general information about companies (such as information directed to investors or to current/prospective employees), including financial data, descriptions of research and development programmes, and discussion of regulatory developments affecting the company and its products. Also, in the EFPIA Code, Guidelines for Internet Websites Available to Healthcare Professionals, Patients and the Public in the EU, it stated 'General information on the company. Websites may contain information that would be of interest to investors, the news media and the general public, including financial data, descriptions of research and development programmes, discussion of regulatory developments affecting the company and its products, information for prospective employees, etc. The content of this information is not regulated by these guidelines or provisions of medicines advertising law.'

Given the above, GlaxoSmithKline submitted that the release was not promotional material under the scope of the Code. Additionally the Code made provision for such information to be made available and reviewed to ensure that it was balanced. As such GlaxoSmithKline respectfully suggested that there was no prima facie case to answer.

Notwithstanding its position that there was no prima facie case, GlaxoSmithKline addressed each of Takeda's

points individually. However in the context of a press release for business and financial media these statements could not be viewed under the Code in the same way as promotional claims, they were a balanced and truthful reflection of a company's presentation of data to the US regulatory authorities that had been examined in accordance with the supplementary information to Clauses 20.2 and 14.3 in the knowledge that the release dealt with a significant corporate newsworthy event occurring in the US with a probable material impact on the share price.

'Avandia is the most widely studied oral anti-diabetic medicine for the treatment of Type 2 diabetes. The extensive data base for Avandia includes…'

All of the 116 trials cited in the press release were publicly accessible on the GlaxoSmithKline CTR: http://ctr.gsk.co.uk. As no promotional claims were made, it was not necessary to cite each study individually as would be the case with promotional material. Given the focus of the FDA's review of cardiovascular outcome data which could only be fully determined through long-term studies, it was entirely appropriate that DREAM, ADOPT and RECORD be mentioned in the press release as they contained important safety data pertinent to the FDA hearing. The trials mentioned were an accurate reflection of how the data was presented at the FDA hearing. In the context of a safety discussion, it was important to consider the totality of the data. The regulatory authorities explicitly asked that all data be submitted for review including studies conducted on out of licence populations, such as DREAM.

The labelling for any medicine reflected the totality of the data regarding safety. For example, a study that included patients with heart failure was reflected in the SPC and was out of licence, yet contributed important information to the SPC and formed the basis of the contraindication in heart failure in Europe and the different warnings and contraindications that appeared in the US labelling.

GlaxoSmithKline noted that the ADOPT study, referred to by Takeda, was not an out of licence population in the US where the FDA Advisory Committee occurred. The US label indications were as follows

'Avandia is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus.

- Avandia is indicated as monotherapy.
- Avandia is also indicated for use in combination with a sulfonylurea, metformin, or insulin when diet, exercise, and a single agent do not result in adequate glycaemic control. For patients inadequately controlled with a maximum dose of a sulfonylurea or metformin, Avandia should be added to, rather than substituted for, a sulfonylurea or metformin.
- Avandia is also indicated for use in combination with a sulfonylurea plus metformin when diet, exercise, and both agents do not result in adequate glycaemic control.'

For completeness GlaxoSmithKline provided the US prescribing information for Avandia.

Therefore GlaxoSmithKline strongly disagreed that this statement in the context of a press release relating directly to a company presentation to the US regulatory body that was in the public domain was in any way a breach of the multiple alleged breaches of the Code.

'Across the extensive dataset for Avandia, there is no consistent or systematic evidence that Avandia increases the risk of heart attack or cardiovascular death in comparison with other antidiabetic medicines'

GlaxoSmithKline disagreed with Takeda's allegation that this was a claim; it was a statement in an important and relevant press release to business media.

The press release was an accurate summary of the data presented and GlaxoSmithKline's position on that data to the FDA Advisory Committee meeting. This meeting focused on the safety data for rosiglitazone. It was important that the data was discussed in terms of the definitions used in clinical trials, from where the data originated. In the clinical trials presented by GlaxoSmithKline, the definition of cardiac ischaemia was broad and included symptoms, such as dyspnoea (shortness of breath). In the GlaxoSmithKline presentation, the number of myocardial infarctions or cardiovascular deaths on rosiglitazone was small, crossed '1' on the Forest plot, and hence was not significant. Therefore based on the data presented this was an acceptable statement to make at the FDA Advisory Committee.

Takeda alleged that this statement was not consistent with the UK SPC. As previously stated this press release was based entirely on events relating to the US and FDA Advisory Committee with share price relevance in the UK and US – it would not therefore be appropriate to base this information on the UK SPC (which differed from the US prescribing information).

Unfortunately Takeda had also selectively quoted and selectively highlighted the Avandia SPC. It had omitted that in section 4.8, with reference to cardiac ischaemia, there was the following note: 'The frequency category for the background incidence of these events, as taken from placebo group data from clinical trials, is 'common".

Comments on the FDA Advisory Committee vote were not included in the press release as its purpose was to summarise the data, and GlaxoSmithKline's position on it, to investors and business journalists that GlaxoSmithKline presented to the FDA Advisory Committee, and as mentioned above was issued before the meeting started. This fulfilled GlaxoSmithKline's corporate obligation to disclose information to investors that the company knew of and which might materially affect its share price. A subsequent stock exchange announcement posted later the same day after the Advisory Committee meeting had finished detailed the results of the Committee's votes and deliberations regarding the cardiovascular position of

Avandia. This reflected the position the Committee took and importantly reflected that the Committee declined to comment on comparative risk of Avandia to other oral anti-diabetic medicines. Takeda did not mention this in its complaint.

GlaxoSmithKline strongly refuted the allegation that the press release did not encourage the rational use of Avandia as the press release was not intended for prescribers, the purpose and source of the data within the press release was clearly stated, the information was a fair and balanced reflection of that data and a subsequent stock exchange announcement the same day detailed the Advisory Committee's findings.

GlaxoSmithKline also noted the following:

- The US licence did not list cardiac ischaemia as a common adverse event. GlaxoSmithKline reiterated that as the press release reported on data presented to the US regulatory body, therefore it was appropriate that it was based on the US licence.
- The FDA Advisory Committee queried whether the available data supported a conclusion that Avandia increased cardiac ischaemic risk in type 2 diabetes mellitus?If it did, was there evidence that this risk was greater than other available therapies for the treatment of type 2 diabetes mellitus?
  It did not vote specifically on myocardial infarction and myocardial ischaemia, but the broader definition as noted above. It did not vote definitively on the second part of the question at that stage. It also noted during the meeting that the comparison to placebo was not as relevant to clinical practice as the comparison to other treatments.
  The minutes stated that many committee members were reluctant to draw conclusions comparing the risk level of Avandia versus other available therapies, until additional [sic] has been reviewed (eg Takeda's study of pioglitazone).
- GlaxoSmithKline's analysis was versus comparator treatments and not placebo and hence comments on placebo were not included in the press release. Therefore it was entirely appropriate for the press release to reflect comparator treatments as it reflected GlaxoSmithKline's presentation of the data.
- The Advisory Committee made recommendations to the FDA. The FDA was currently reviewing the evidence and the deliberations of the Advisory Committee and had not yet decided upon what (if any) action would be taken with regard to labelling in the US.
- With regard to UK regulatory perspective, the Medicines and Healthcare products Regulatory Agency (MHRA) described the increased risk of myocardial infarction and cardiovascular death as 'small' and it stated that 'In September 2006, following a comprehensive review within Europe of the available data from clinical trials, the product information for prescribers and patients was updated to reflect more fully the risk of heart failure and to include a warning about the potential small increased risk of myocardial infarction in patients receiving rosiglitazone compared with those receiving placebo (dummy pills).'

The MHRA, together with EU regulatory agencies, was currently reviewing all the available data for the cardiovascular safety of rosiglitazone and pioglitazone.

Consequently GlaxoSmithKline did not believe that this statement, in the context of the above, breached the Code. GlaxoSmithKline refuted any breach of the Code in terms of the statements made in the context of a corporate press release regarding a US regulatory process.

'Myocardial ischaemia: There was no statistically significant increase in myocardial ischaemia in ADOPT, GlaxoSmithKline's long term comparator study'

GlaxoSmithKline again submitted this was not a claim but a statement made in the appropriate context outlined above.

Of all the trials that had been conducted on rosiglitazone, large scale, long-term clinical trials in patients with the disease were the most scientifically rigorous way of assessing the risk of myocardial ischaemia. ADOPT (A Diabetes Outcome Progression Trial) directly compared both the safety and effectiveness of Avandia with metformin and a sulphonylurea (glibenclamide) – two of the most commonly used medicines to treat type 2 diabetes, in over 4,300 patients studied for up to 6 years. Results showed that the overall risk of serious, cardiovascular events (CV death, myocardial infarction, and stroke, or major adverse cardiovascular events (MACE) endpoint prospectively defined) for patients on Avandia was comparable to metformin and a sulphonylurea (glibenclamide). These data were post-adjudicated by three independent cardiologists. ADOPT showed comparable rates of cardiovascular deaths between the agents under study. Although not powered to assess cardiovascular risk, it was the only trial on rosiglitazone to date that could add significantly to what was known about the safety profile of rosiglitazone. Clearly long-term prospective trials contributed significantly to the information about the safety of medicines. RECORD, which was designed to look at cardiovascular risk, had not reported y*et al*though an interim analysis showed no significant difference in cardiovascular risk compared with metformin or sulphonylureas, except for the well-known risk of cardiac failure, in which rosiglitazone was contraindicated.

In the context of a safety discussion, it was important to include all data sources and specifically long-term trials which provided more robust data on the safety and efficacy of a medicine.

As discussed above the ADOPT study was consistent with the US labelled population, and as such Takeda's reference to the European SPC not relevant.

GlaxoSmithKline did not believe that this statement in the context of a press release outlined above in any

way breached the Code. GlaxoSmithKline refuted any breach of the Code in terms of the statements made in the context of a corporate press release regarding a US regulatory process.

'Heart Attack: the number of heart attacks across the sources of data is small, the data are inconsistent, and the totality of the evidence does not show any difference between Avandia and the most commonly prescribed anti-diabetic agents. In three epidemiological database studies, the risk of heart attack was similar for Avandia compared to the other anti-diabetic agents, and in one database study comparing Avandia to Actos, there was no difference.'

The data were inconsistent which was why the FDA Advisory Committee was called to discuss them. As stated above, the MHRA described the increased risk of myocardial infarction and cardiovascular death as 'small'.

The Nested Case-Control study to which Takeda referred compared rosiglitazone with other anti-diabetic agents excluding pioglitazone, and separately compared pioglitazone with other anti-diabetic agents excluding rosiglitazone. There was no comparison of rosiglitazone with pioglitazone. This study was not a direct comparison of Actos and Avandia as stated by Takeda.

There was only one observational study, the Pharmetrics study, which was submitted to the FDA by GlaxoSmithKline. External sources presented other observational studies which directly compared rosiglitazone and pioglitazone, and showed no difference.

GlaxoSmithKline strongly disagreed that the press release gave false and misleading information regarding other medicines or disparaged other medicines. The press release focused on rosiglitazone. GlaxoSmithKline refuted any breach of the Code in terms of the statements made in the context of a corporate press release regarding a US regulatory process.

'CV death: the long term trials provide no evidence of increase CV death or all cause mortality with Avandia compared to the most commonly prescribed oral antidiabetics'

GlaxoSmithKline disagreed that in the context of a corporate press release relating to a US regulatory process this is a promotional claim under the terms of the Code.

The Nissen and Wolski meta-analysis showed a non-significant difference in the odds ratio for death from cardiovascular causes (95% CI, 0.98-2.74; P=0.06). Takeda erroneously cited this p value as having borderline significance; however independent interpretation and convention would state that no statistical difference was seen. Even using the results of this highly controversial meta-analysis, GlaxoSmithKline was correct to state that there was no evidence of increased CV death. It was important to note some of the methodological issues with this meta-analysis. Of particular importance to cardiovascular death, this meta-analysis did not contain patient level data and so it was not possible to adjudicate the cause of death and, by their own admission, the authors excluded several studies where no cardiovascular events were seen.

The most robust prospective analysis of rosiglitazone with respect to cardiovascular death was conducted by GlaxoSmithKline using adjudicated endpoints from the three long-term rosiglitazone outcome studies, DREAM, ADOPTand RECORD. When more than 14,000 patients across the three studies were evaluated, the hazard ratio for death was 0.84 (0.57-1.22). This data was reviewed as part of the Advisory Committee.

GlaxoSmithKline was extremely disappointed by Takeda's comments regarding the conclusions of health professionals working in the field of diabetes. This could only be anecdotal reports and these unsupported comments could not be seen as a robust interpretation of the entirety of the data as presented to the FDA. Nissen and Wolski had been widely criticised, for example the editor of The Lancet on 2 June 2007 stated that 'Until the results of RECORD are in, it would be premature to overinterpret a meta-analysis that the authors and [New England Journal of Medicine] editorialists all acknowledge contains important weaknesses'. In various letters to the New England Journal of Medicine, health professionals working in the field of diabetes criticised the methodology or conclusions of Nissen and Wolski. Furthermore, the conclusions of the meta-analysis had been disputed in Nature Clinical practice (Gerstein and Yusuf 2007).

To add further context to the discussion, Lago *et al* (2007) assessed the risk of heart failure and cardiovascular death in a meta-analysis of studies which specifically adjudicated cardiovascular endpoints or adverse events and found no difference between rosiglitazone and pioglitazone. 'The risk for congestive heart failure did not differ for rosiglitazone and pioglitazone (1·74, 0·97–3·14, p=0·07). The risk of cardiovascular death did not differ between both drug groups (1·01, 0·73–1·40, p=0·96)'.

GlaxoSmithKline additionally referred back to its response above regarding the absence of any comment on comparison with placebo.

GlaxoSmithKline strongly disagreed that this statement in the context of this press release breached the Code in anyway. GlaxoSmithKline refuted any breach of the Code in terms of the statements made in the context of a corporate press release regarding a US regulatory process.

'Stroke: Across the data sources, fewer strokes are observed with Avandia than with other anti-diabetic medicines, although the differences in the long-term trials were not statistically significant'

As stated previously this was not a promotional claim. This press release represented company data presented

to a FDA advisory committee, therefore it was entirely possible that data would be presented that was not published.

In GlaxoSmithKline's presentation to the FDA, the integrated clinical trials analysis (ICT) showed a significant decrease in stroke with rosiglitazone compared with other anti-diabetic medicines. When these data were integrated with data from DREAM and ADOPT, a numerical trend was seen, but as rightly noted in the presentation to the Advisory Committee and the press release, the result was not significant. This statement was an accurate reflection of the data GlaxoSmithKline presented to the FDA Advisory Committee. This data was presented to the regulatory authority as it was important information relating to the safety profile of rosiglitazone. As stated previously, the purpose of the press release was to report an accurate, fair and balanced summary of the data GlaxoSmithKline presented to the FDA to investors. This was not a promotional piece and hence this was not a claim. GlaxoSmithKline had not made any promotional claims regarding any benefit on stroke.

Therefore GlaxoSmithKline disputed that there was any breach of the Code. GlaxoSmithKline refuted any breach of the Code in terms of the statements made in the context of a corporate press release regarding a US regulatory process.

'GlaxoSmithKline continues to support Avandia as safe and effective when used appropriately'

This was not a promotional item and hence this was not a claim. Additionally the release was not directed to health professionals or the public. The FDA Advisory Committee hearing specifically discussed the safety of Avandia. It would be very difficult to clearly report GlaxoSmithKline's position on this meeting to a financial (non-medical) audience in other terms. The audience would not necessarily understand the medical term one would use to replace this word. Additionally, the word 'safe' had been qualified by the phrase 'when used appropriately'. GlaxoSmithKline believed it was acceptable to state its position in a press release to the business and financial media. GlaxoSmithKline would not use such a statement in promotional items.

GlaxoSmithKline disagreed that this statement was a breach of the Code. The company reiterated that the press release was not intended for healthcare providers or patients so Takeda's allegation that GlaxoSmithKline had not encouraged the rational use of its products was completely false. GlaxoSmithKline refuted any breach of the Code in terms of the statements made in the context of a corporate press release regarding a US regulatory process.

Important safety Information for Avandia (rosiglitazone maleate)

As stated previously this press release was solely based on events in the US, placed there by the US arm of the company. GlaxoSmithKline was legally obliged to include this information in a US press release and to provide it in layman's language. It was based on the US licence as the press release was regarding data presented to the US regulatory authorities. GlaxoSmithKline completely refuted the allegation that this was directed at or intended for patients.

GlaxoSmithKline also strongly disagreed with Takeda's allegation that '…clearly promoting Avandia to patients in the UK and Europe'. This was not the intention of any press release that was placed on GlaxoSmithKline's corporate website.

GlaxoSmithKline noted Takeda's comment '….it is misleading with respect to the safety of the product'. This suggested that GlaxoSmithKline intentionally misled the FDA Advisory Committee which was an extremely serious allegation that if true would have personal and criminal consequences for GlaxoSmithKline's senior executive who presented that data. GlaxoSmithKline strongly refuted this allegation. GlaxoSmithKline was committed to patient safety and transparency in its data. This press release accurately reflected the presentation given by GlaxoSmithKline at the FDA meeting in a fair and balanced way. GlaxoSmithKline communicated in an appropriate way with health professionals and patients especially with regard to product safety and not through press releases posted on the corporate website clearly intended for investor media that were labelled as such.

GlaxoSmithKline had stated that this press release was issued by the US arm of the company and posted on the corporate website. In response to Takeda's final comments GlaxoSmithKline noted the following:

1 GlaxoSmithKline was a UK headquartered company, thus it was no surprise that the website was UK based. The UK address of the company's registered office was on the bottom of all pages on the corporate website. There was a specific US Pharmaceuticals website as noted by Takeda, however it omitted to mention that there was a UK Pharmaceuticals website also at www.gsk.co.uk; the latter did not contain any of the corporate page links that were seen on www.gsk.com, thus distinguishing it from the corporate pages.
2 Visiting www.gsk.co.uk directed the reader to the UK company website, which referred to the UK Pharmaceuticals Stockley Park office.
3 Navigating from the UK specific site for career opportunities did indeed take the reader to the corporate site. GlaxoSmithKline was a major employer in the UK with worldwide career opportunities and so it was no surprise that the corporate site hosted all of GlaxoSmithKline's recruitment pages.
4 The position of GlaxoSmithKline UK's website was made clear above. If an individual were to 'Google' GlaxoSmithKline they would find the corporate website which reflected GlaxoSmithKline's corporate position. If they wished to find www.gsk.co.uk GlaxoSmithKline expected that this would be typed into the address bar of the browser rather than a search engine. Nevertheless having repeated Takeda's Google search the following was found as the closest match.

United Kingdom - GlaxoSmithKline Worldwide - GlaxoSmithKline
About GlaxoSmithKline summarizes the mission of GlaxoSmithKline and provides users with an overview of the organization and biographies of its Board of Directors and Corporate ...
www.gsk.com/worldwide/uk.htm - 9k

Clicking on the url, took the reader to the same site as www.gsk.co.uk. If a reader was at www.gsk.com there was a box on the front page that invited readers to click to 'Find contact details for GlaxoSmithKline offices around the world'. This link took readers to a listing of countries which was headed by the UK. This too took the reader to the same page as www.gsk.co.uk which contained no press releases.

5 Takeda was correct that the London Stock Exchange (and New York Stock Exchange) prices were given on the front page of its corporate website. GlaxoSmithKline failed to see that this was relevant to the position of GlaxoSmithKline UK, and if anything reinforced its fundamental argument about Takeda's misperception regarding this release and the role of the corporate site.

Takeda questioned the media contacts listed on the press release. They were in fact all corporate media contacts, whose role was to liaise with business and financial media only. This included all global business and financial media.

None of the contacts listed had anything to do with the UK operating company or UK health professionals. All were based at corporate headquarters in the UK.

GlaxoSmithKline noted that Takeda had not referred to the US media contact names also cited on this release.

GlaxoSmithKline was a UK headquartered company which had been exposed to significant publicity regarding the safety of Avandia. This was material to investors given the impact on the share price as detailed above. Events in the US related to this were thus pertinent to investors who should rightly be informed of the company's position regarding the data and its impact.

GlaxoSmithKline found Takeda's position surprising, in that it alleged multiple breaches of the Code for a corporate press release, directed to and labelled as a business release that clearly had business relevant content for one of GlaxoSmithKline's major products. It clearly followed that this was share price relevant information given the events since 21 May when the Nissen and Wolski meta analysis was published. The release referred to regulatory events occurring in the US that were relevant to the US Prescribing Information rather than the European SPC. Given the clarity of the position, GlaxoSmithKline questioned Takeda's motivation for making such an extensive complaint.

In summary GlaxoSmithKline referred to Clause 21.1 which stated, 'Access to **promotional** material directed to a **UK audience** provided on the internet in relation to prescription only medicines should generally be limited to health professionals and appropriate administrative staff' (emphasis added).

Clause 21.2 referred to 'Information or promotional material …. covered by Clause 21.1 …'.

Given the specificity of Clause 21 in this regard, GlaxoSmithKline did not believe that this corporate press release, on GlaxoSmithKline's corporate website, relating to an event in the US could be deemed promotional when it was clearly investor relevant information and was labelled as such on the website page where the link was present. Additionally the release itself was labelled as being from the US office, and all of the individuals named as media contacts were employed in GlaxoSmithKline's corporate office.

GlaxoSmithKline strongly refuted all allegations of breaches of the Code and other wrongdoing as alleged, and respectfully suggested that there was no prima facie case to answer.

PANEL RULING

The Panel noted that much was made about whether the press release was promotional or not and whether the press release was covered by the clauses of the Code. The Panel noted that the supplementary information to Clause 20.2, Information to the public, made it clear that other Clauses of the Code also applied to information to the public.

The Panel noted GlaxoSmithKline's suggestion that there was no prima facie case to answer. This was a matter for the Director to decide prior to referral to the Code of Practice Panel. The Director had decided there was a prima facie case for GlaxoSmithKline to answer and thus the material was before the Panel for consideration.

The Panel examined the press release noting that it had been placed on the corporate website by GlaxoSmithKline US. It had been sent to UK financial media. The press release covered the FDA Advisory Committee which had occurred in the US and related to the US regulatory authorities. The data would obviously be of interest worldwide. The important safety information provided at the end of the press release related to the use of Avandia in the US.

The Panel noted that there had originally been two closely similar versions of the press release on the website. That accessed via 'Avandia News' did not originally feature the heading stating the intended audience. This was remedied by GlaxoSmithKline during inter-company dialogue.

GlaxoSmithKline was a UK headquartered company. It was not unreasonable for UK corporate contact details for the UK media to be included on the press release. The press release was issued in the UK to business/financial journalists, investors and analysts only. The issue would be relevant to such an audience.

The Panel noted Clause 21.2 which stated that

'Information or promotional material about medicines covered by Clause 21.1 above which is placed on the Internet outside the UK will be regarded as coming within the scope of the Code if it was placed there by a UK company or at the instigation or with the authority of such a company and it makes specific reference to the availability or use of the medicine in the UK.'

The Panel considered that information about a prescription only medicine had been placed on the Internet by a UK company or an affiliate or at the instigation or with the authority of such a company. The second part of the clause required specific reference to the availability or use of the medicine in the UK. The Panel noted that the press release at issue referred to Avandia which was available in the UK. It included general information about Avandia but did not specifically refer to its availability or use in the UK. On the contrary the inclusion of important safety information related to the use of the product in the US. The press release related to a particular meeting of the FDA Advisory Committee and was issued as a corporate press release. The Panel did not consider that the press release at issue met both the requirements of Clause 21.2 and thus there was no breach of that clause. This meant that the press release was not within the scope of the Code. The other allegations made by Takeda were as a consequence ruled not to be in breach of the Code including of Clause 2.

During its consideration of this case, the Panel noted that Takeda had referred to the EFPIA Code. The Panel could not make any rulings regarding the EFPIA Code as it had no locus to do so. National associations such as the ABPI were obliged as members of EFPIA to incorporate the requirements of the EFPIA Code into their local codes as far as national law permitted.

Complaint received 20 September 2007

Case completed 11 January 2008

MEMBER OF THE PUBLIC v ROCHE

MabThera journal advertisement

A member of the public complained about a Roche advertisement for MabThera (rituximab) in the BMJ.

The complainant had retired from the legal/academic profession and was not medically qualified but had access to the BMJ via a relative. As he had rheumatoid arthritis he was naturally drawn to the MabThera advertisement and thought it was misleading by portraying a rheumatoid arthritis patient performing high jump like a professional athlete. Unfortunately patients who needed further medicines after failure of first line treatment, were far from this level. The advertisement raised unsubstantiable hopes for patients and might cause them frustration and disappointment.

Moreover, to use the National Institute of Health and Clinical Excellence (NICE) as a recommendation with gold medal was surely out of line and against the requirement of the Code which forbade quoting official bodies in promotional material.

The Panel noted that the advertisement, which featured a black and white photograph of an athlete performing a 'Fosbury flop' over a high jump rail, was headed 'The day perceptions changed'. The Panel did not consider that the majority of health professionals, to whom the advertisement was directed, would assume that MabThera treatment would enable rheumatoid arthritis patients to be similarly athletic. The Panel noted Roche's submission that the image and headline had been chosen to represent the situation where a paradigm shift in the approach or thinking about a certain situation had resulted in progress. MabThera was a new approach to the treatment of rheumatoid arthritis. The Panel did not consider that the advertisement was misleading as alleged. No breach of the Code was ruled.

The advertisement included the claim 'Recommended by NICE'. Although the Code prohibited reference to certain bodies in promotional material, NICE was not one of them. No breach was ruled.

The BMJ was primarily aimed at health professionals. Although members of the public might see the publication, the BMJ was not aimed at the public and so in that regard the advertisement would not give rise to unfounded hopes of successful treatment. No breach was ruled.

A member of the public complained about an advertisement for MabThera (rituximab) which placed by Roche Products Ltd in the BMJ, 29 September.

COMPLAINT

The complainant stated that he had retired from the legal/academic profession and was not medically qualified but had access to the BMJ via a relative. As he had rheumatoid arthritis he was naturally drawn to the MabThera advertisement. He thought this advertisement was quite misleading by portraying a rheumatoid arthritis patient performing high jump like a professional athlete. Unfortunately rheumatoid arthritis patients in his condition, who needed further medicines after failure of first line treatment, were far from this level. The advertisement raised unsubstantiable hopes for patients and might cause them frustration and disappointment.

Moreover, to use the National Institute of Health and Clinical Excellence (NICE) as a recommendation with gold medal was surely out of line and against the specific requirement of the Code, which forbade quoting official bodies in promotional material.

When writing to Roche, the Authority asked it to respond in relation to Clauses 7.2, 7.8, 9.5, and 20.2 of the Code.

RESPONSE

Roche stated that the advertisement at issue was placed in the BMJ as an insert and was produced in accordance with the Code.

The BMJ was intended for health professionals via subscription. It was not available directly to the public and in the complainant's case they obtained it from a friend or relative. The advertisement was placed in this professional journal and as such should not have knowingly breached Clause 20.2.

With regard to the image used in the advertisement, the use of a professional athlete had not been done to infer that patients taking MabThera would be able to high jump, rather it represented a well known paradigm shift where changing the approach or thinking about a certain situation had resulted in progress.

The use of a high jumper performing a 'Fosbury flop' was purposeful. Before the 1968 Olympics, athletes approached the high jump with something called a 'Western Roll'. This limited their ability to get above 2.4m; however, with the advent of softer mats Dick Fosbury initiated a backward roll over the bar nicknamed the 'Fosbury flop' which changed the paradigm in the jumping technique for the high jumper and resulted in the 2.4m barrier being broken.

Until recently, the perception that rheumatoid arthritis was primarily T cell driven was largely accepted across the rheumatology community. MabThera acted by depleting B cells and thus an agent that acted on B cells rather than either directly or indirectly on T cells had caused a shift in perceptions as to the pathophysiology of the disease. The title of the advertisement, 'The day perceptions changed', indicated the analogy.

Roche did not intend to imply that if a patient was prescribed MabThera they would be jumping the high jump and it strongly contested that the advertisement and its layout were in breach of Clauses 7.2 or 7.8. Roche also did not believe that a health professional (the target of the advertisement) would come to the same conclusion as the complainant. This was based on market research testing with the image prior to use. Roche also noted that the licence for MabThera was for patients who had previously failed the gold standard treatments, the anti TNF agents, and thus MabThera now offered a therapeutic option for patients who would otherwise have had limited or no option other than palliative treatment.

Referring to the complainant's concerns regarding the fact that MabThera had been recommended by NICE and that a statement to this effect appeared in the advertisement, Roche did not believe that this was in breach of Clause 9.5 as NICE did not fall within the agencies referred to within that clause. It was also of significant interest to prescribers who looked to NICE for guidance on rational medicine use. The use of a medal was in keeping with the image used.

PANEL RULING

The Panel noted that the advertisement, which featured a black and white photograph of an athlete performing a 'Fosbury flop' over a high jump rail, was headed 'The day perceptions changed'. The advertisement had been placed in the BMJ and the Panel did not consider that the majority of health professionals, to whom the advertisement was directed, would assume that MabThera treatment would enable rheumatoid arthritis patients to be similarly athletic. The Panel noted Roche's submission that the image and headline had been chosen to represent the situation where a paradigm shift in the approach or thinking about a certain situation had resulted in progress. MabThera was a new approach to the treatment of rheumatoid arthritis. The Panel did not consider that the advertisement was misleading as alleged. No breach of Clauses 7.2 and 7.8 was ruled.

The Panel noted that the advertisement included the claim 'Recommended by NICE'. Although Clause 9.5 prohibited reference to certain bodies in promotional material, NICE was not one of them. No breach of Clause 9.5 was ruled.

The advertisement at issue appeared in the BMJ ie a journal primarily aimed at health professionals. Although members of the public might see the publication (either by buying the print version or on the internet), the BMJ was not aimed at the public and so in that regard the advertisement would not give rise to unfounded hopes of successful treatment. No breach of Clause 20.2 was ruled.

During its consideration of this case the Panel noted the depiction of a gold, Olympic type medal which referred to NICE. In that regard the Panel was concerned that the advertisement implied that MabThera was a 'winning' medicine ie more effective in rheumatoid arthritis than any other. The Panel considered that this might be an exaggerated claim and asked that Roche be advised of its concerns in this regard.

Complaint received	**1 October 2007**
Case completed	**5 November 2007**

CASE AUTH/2053/10/07 *NO BREACH OF THE CODE*

GLAXOSMITHKLINE v ASTRAZENECA

Symbicort leavepiece

GlaxoSmithKline complained about a Symbicort (budesonide/formoterol) leavepiece, issued by AstraZeneca, which explained Symbicort SMART (Symbicort Maintenance and Reliever Therapy in one inhaler) therapy and in that regard contained the statement 'Rx Symbicort 200/6 1 inhalation bd plus as needed*'. The asterisk referred the reader to the summary of product characteristics (SPC) and to the fact that Symbicort 'as needed' was not indicated for prophylactic use prior to exercise. GlaxoSmithKline considered that use of the asterisk acknowledged that there was important information that prescribers needed to know.

The Symbicort SMART regimen was a novel approach to treating asthma and therefore something that prescribers were not familiar with; there was thus a responsibility to provide adequate and visible safety information. The complexity and restrictions of the regimen were glossed over by the simple, unqualified statement 'Rx Symbicort 200/6 1 inhalation bd plus as needed' which implied that there was no upper limit to such a regimen and was inconsistent with the SPC. GlaxoSmithKline alleged that the statement was unbalanced, misleading and did not encourage rational use.

The Panel noted that the statement at issue 'Rx Symbicort 200/6 1 inhalation bd plus as needed' appeared as facsimile handwriting to mimic a prescription. The asterisk referred readers to the SPC and reminded them that Symbicort as needed was not indicated for prophylactic use prior to exercise. Section 4.2 of the SPC (Posology and method of administration) stated that, with regard to maintenance and reliever therapy, patients should take a daily maintenance dose of Symbicort and in addition take Symbicort as needed in response to symptoms.

The Panel considered that the statement accurately reflected the dosage particulars listed in the SPC. It would be unlikely that a prescriber would copy the statement in the leavepiece without seeking further information and advising a patient accordingly. In the Panel's view prescribers would be familiar with the use of medicines such as Symbicort and well aware of the need to act if patients asked for too many repeat prescriptions ie over-used their inhalers. The Panel considered that given the audience to which it was directed, the statement was not unbalanced, misleading or exaggerated as alleged. Further, the Panel did not consider that the statement was such that it did not encourage the rational use of Symbicort. No breach of the Code was ruled.

GlaxoSmithKline UK Ltd complained about a Symbicort (budesonide/formoterol) leavepiece (ref SYMB 07 11774) issued by AstraZeneca UK Limited which explained Symbicort SMART (Symbicort Maintenance And Reliever Therapy in one inhaler) therapy.

COMPLAINT

GlaxoSmithKline noted that the leavepiece contained the statement 'Rx Symbicort 200/6 1 inhalation bd plus as needed*'. The asterisk referred the reader to the summary of product characteristics (SPC) and related to the fact that Symbicort 'as needed' was not indicated for prophylactic use prior to exercise. Its presence acknowledged that there was important information that prescribers needed to know.

GlaxoSmithKline was concerned that the statement was unbalanced, exaggerated and misleading. GlaxoSmithKline considered that there needed to be some qualification within or immediately associated with the statement in accordance with the supplementary information to Clause 7 of the Code.

The Symbicort SMART regimen was a novel approach to treating asthma; the complexity and restrictions of the regimen were glossed over by the simplified statement at issue. Being a novel regimen, it was something that prescribers were not familiar with; hence there was a responsibility to provide adequate and visible safety information.

The leavepiece made no attempt to specify a safe upper limit on the number of 'as-needed' inhalations which was stipulated in the SPC. The following statement was taken directly from section 4.2 of the SPC for the Symbicort 100/6 and 200/6 Turbohaler (GlaxoSmithKline emboldening added for convenience):

- The recommended maintenance dose is 2 inhalations per day, given either as one inhalation in the morning and evening or as 2 inhalations in either the morning or evening. Patients should take 1 additional inhalation as needed in response to symptoms. If symptoms persist after a few minutes, an additional inhalation should be taken. **Not more than 6 inhalations should be taken on any single occasion.**

- A total daily dose of more than 8 inhalations is not normally needed; however, a total daily dose of up to 12 inhalations could be used for a limited period. **Patients using more than 8 inhalations daily should be strongly recommended to seek medical advice.** They should be reassessed and their maintenance therapy should be reconsidered.

The unqualified statement 'Rx Symbicort 200/6 1 inhalation bd plus as needed' implied that there was no upper limit to such a regimen and was inconsistent with the SPC.

In inter-company correspondence AstraZeneca had stated that there was no need to include the dosage limits because had this been significant safety information, it would have been included in the 'Special warnings and precautions for use' section of the SPC. GlaxoSmithKline disagreed with this position and believed that the provision of information on any medicines must be conducted ethically and in the context of the prescribers' knowledge of the product/regimen, with patient safety at its core. It was not reasonable to refer to where safety information was placed in the SPC. In fact, section 4.4 'Special warnings and precautions for use' of the Symbicort SPC stated:

- If patients find the treatment ineffective, or exceed the highest recommended dose of Symbicort, medical attention must be sought (see section 4.2 'Posology and method of administration').

In addition, section 4.2 'Posology and method of administration' stated:

- Close monitoring for dose-related adverse effects is needed in patients who frequently take high numbers of Symbicort as-needed inhalations.

GlaxoSmithKline believed that both of the above statements indicated that the limit on the number of 'as-needed' inhalations was considered important enough to be made clear in promotional material to ensure prescribers were aware of appropriate use of the SMART regime.

In inter-company correspondence AstraZeneca had stated that 'Rx Symbicort 200/6 1 inhalation bd plus as needed' was not a claim and therefore further qualification was not required. GlaxoSmithKline disagreed; this statement appeared as an instruction to prescribers, written in a style to mimic a doctor's prescription in a piece of promotional literature. If, as claimed by AstraZeneca, the leavepiece was not intended as comprehensive dosing information but was meant to provide background information to make physicians aware of the significance of over-relying on short acting bronchodilators, then the statement 'Rx Symbicort 200/6 1 inhalation bd plus as needed' mimicking a prescription should not appear at all.

Symbicort maintenance and reliever therapy was a novel approach to the treatment of asthma which prescribers might not be familiar with. It was the responsibility of the pharmaceutical industry to provide clear information in this case regarding the dosage limits to ensure patient safety.

GlaxoSmithKline alleged that the statement 'Rx Symbicort 200/6 1 inhalation bd plus as needed' was unbalanced, misleading and did not encourage the rational use of the medicine, in breach of Clauses 7.2 and 7.10.

RESPONSE

AstraZeneca disagreed that the statement at issue was a claim. The statement was included in the leavepiece because it was essential for prescribers to know how a prescription for Symbicort as maintenance and reliever therapy should be written. A single inhaler used both as maintenance therapy and additionally for the relief of symptoms was a new concept in the management of asthma. The statement 'plus as needed' was agreed in the course of the European Mutual Recognition Process and was stated in section 4.1 of the Symbicort 200/6 SPC. Without clearly telling prescribers how a prescription should be written it was thought that prescriptions might not be correctly understood and in some cases invalid prescriptions such as 'Rx Symbicort SMART …' would have been written.

An asterisk and a footnote which referred to the SPC was included in the leavepiece as 'Symbicort 200/6 1 inhalation bd plus as needed' was the most widely studied dose and considered the usual treatment regimen for the majority of patients. It was not the only licensed dose or strength. Additionally, AstraZeneca indicated to the prescriber that while Symbicort was approved for 'reliever' use it should not be used for regular prophylactic use.

AstraZeneca noted GlaxoSmithKline's comments that 'Rx Symbicort 200/6' implied that there was no upper limit to such a regimen and therefore it was inconsistent with the SPC. Furthermore, GlaxoSmithKline recognised that the asterix was there as an acknowledgement that important information was available which prescribers needed to know.

All medicines had safe upper dosing limits and these were as stated in the SPC, referred to in the leavepiece, together with other important information which prescribers needed to know.

The Medicines and Healthcare products Regulatory Agency (MHRA) was particular about the inclusion of all relevant statements with regard to the safe use of products yet in pre-vetting AstraZeneca's materials it had not commented about the need to present additional information in the leavepiece.

AstraZeneca noted that GlaxoSmithKline had drawn attention to section 4.2 'Posology and method of administration' of the SPC and seemed to suggest that these two sentences should be reproduced in all promotional materials. If the detail of the posology and method of administration section of the SPC had to be reproduced in promotional materials this would have profound implications for the industry in general. AstraZeneca noted the context in which these statements were included in section 4.2 of the SPC.

It was well recognized in asthma management that in periods of poor asthma control patients often overused their 'reliever', bronchodilator, when in fact they needed more maintenance corticosteroid. This section provided the rationale for Symbicort as maintenance and reliever therapy, because when the patient had symptoms their use of Symbicort as a 'reliever'

provided additional corticosteroid helping to bring their asthma back under control.

Furthermore, section 4.4 of the SPC stated that 'If patients find the treatment ineffective, or exceed the highest recommended dose of Symbicort, medical attention must be sought'. This statement was a variation of statements included in similar sections of most asthma therapies. In fact the SPC for GlaxoSmithKline's Seretide stated in the same section: 'Serious asthma-related adverse events and exacerbations may occur during treatment with Seretide. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation on Seretide. Increasing use of short-acting bronchodilators to relieve symptoms indicates deterioration of control and patients should be reviewed by a physician'.

AstraZeneca rejected the notion that the full details of the recommended doses of Symbicort, as in the SPC, needed to be listed in promotional materials. In referring to the SPC in the leavepiece, AstraZeneca had responsibly provided clear information as to the correct and judicious use of Symbicort. AstraZeneca recognized its obligations and considered that it had maintained high standards in this and all other materials. AstraZeneca therefore denied that the leavepiece breached the Code as alleged.

PANEL RULING

The Panel noted that the statement at issue 'Rx Symbicort 200/6 1 inhalation bd plus as needed' appeared as facsimile handwriting to mimic a prescription. The asterisk referred readers to the SPC and reminded them that Symbicort as needed was not indicated for prophylactic use prior to exercise. Section 4.2 of the SPC (Posology and method of administration) stated that, with regard to maintenance and reliever therapy, patients should take a daily maintenance dose of Symbicort and in addition take Symbicort as needed in response to symptoms.

The Panel considered that the statement at issue accurately reflected the dosage particulars listed in the SPC. It would be unlikely that a prescriber would copy the statement in the leavepiece without seeking further information and advising a patient accordingly. In the Panel's view prescribers would be familiar with the use of medicines such as Symbicort and well aware of the need to act if patients asked for too many repeat prescriptions ie over-used their inhalers. The Panel considered that given the audience to which it was directed, the statement was not unbalanced, misleading or exaggerated as alleged. No breach of Clause 7.2 was ruled. Further, the Panel did not consider that the statement was such that it did not encourage the rational use of Symbicort. No breach of Clause 7.10 was ruled.

Complaint received	**1 October 2007**
Case completed	**20 November 2007**

CASE AUTH/2054/10/07 *NO BREACH OF THE CODE*

ANONYMOUS v SANOFI-AVENTIS

Representatives' call rates.

An anonymous telephone caller alleged that Sanofi-Aventis was asking its representatives to breach the Code by making their bonus dependant upon them seeing key customers 9-12 times.

The Panel noted that the representatives' briefing material and training slides clearly detailed the requirements of the Code and its supplementary information with regard to call rates ie that the number of calls made by a representative each year should not normally exceed three on average. This did not include attendance at group meetings, including audiovisual presentations, a visit requested by a doctor or other prescribers, a call made in response to a specific enquiry or a visit to follow up a report of an adverse reaction. The Panel thus noted that although a representative might call on a doctor or prescriber three times a year the number of contacts with that health professional in the year might be more than that.

The representatives' briefing material about their incentive scheme referred to activity payments which were based on cumulative targeted activity over a 12 month period. All contacts, face-to-face and all types of meeting contributed to this element. Each time activity payments were referred to representatives were reminded of the requirements of the Code.

A presentation about the incentive scheme contained a slide specifically noting the requirements of the Code with regard to call rates. The slides about targeted activity payments stated that the targets cited referred to all contacts, by the entire team for a specific customer; they were not individual target call rates.

On the basis of the material before it the Panel considered that there was no evidence to show that Sanofi-Aventis had set its representatives contact target call rates outwith the requirements of the Code. No breach of the Code was ruled.

COMPLAINT

An anonymous complainant telephoned the Authority and alleged that Sanofi-Aventis representatives thought that they were being asked to breach Clause 15.4 of the Code with regard to the bonus on seeing a number of key customers 9-12 times. The company was entering a period of redundancy and some managers in one part of England were using short term objectives to look at representatives who were not meeting the 9-12 contact rate and were not receiving the bonus. Leverage was being used unfairly; the objectives were being used to identify poor performance. The complainant stated that this was grossly unfair because of the redundancy phase and a breach of the Code.

The complainant stated that they would not identify themselves for obvious reasons.

When writing to Sanofi-Aventis, the Authority asked it to respond in relation to Clauses 2, 9.1 and 15.4 of the Code.

RESPONSE

Sanofi-Aventis submitted that all of its sales forces were trained on the Code at the start of their initial training course and via the 'I-Learn' training system, to which they also had continuous access as a reference tool. In both cases this training explicitly included the Code requirements on call rates (copies provided).

Additionally, all sales teams were comprehensively briefed on their activities and contact rates with customers. The briefing was based on the requirements of the Code, and specifically Clause 15.4 and its supplementary information. Examples of the current briefing materials which referred to contact frequencies of 9-12 were provided for the sales teams in the cardiovascular and metabolism business units. These were the initial briefing documents distributed to sales staff in early 2007, and the most recent briefing materials used in September 2007 for cycle 3. These all directly referred to and quoted the Code requirements on call frequency. Additional details referred explicitly to the targets as relating to:

- Team targets, not specific to individual representatives. This was briefed verbally to all teams in early 2007 when the targets were launched, and was reinforced in the cycle 3 briefing in September 2007.
- All contacts, not only representative-initiated calls.
- The time period of January – December 2007.

These elements were included to ensure that representatives had a thorough understanding of what was required and that they could satisfy themselves as to its compliance with the Code.

In the latter respect, Sanofi-Aventis' Employee Forum received a query on the Code compliance of the scheme in the first half of 2007. The following extract from the minutes of the Employee Forum meeting of May 2007, published on the company intranet, related to this query:

'Incentivised call rates of 12x per year

> Individuals should discuss any concerns with their RBM/DBM. The incentive scheme has been agreed with [a senior manager] regarding the

input element that is included. The incentive scheme clearly highlights the ABPI Code Clause 15.4 which relates to 'Frequency and Manner of Calls on Doctors and other Prescribers' and representatives must abide by the Code. Contact rates include calls and meetings and the objectives set are for the brand and not an individual representative.'

There had been no further query on these targets which were revisited in the sales meetings in September as described above. It was disappointing that the response above, which encapsulated the current position, was not considered sufficient by the complainant and that they chose to ignore the company policy on 'whistle-blowing', which guaranteed confidentiality of complainants. Equally, Sanofi-Aventis noted that the complainant appeared not to have provided any written material or evidence to substantiate their claim of a breach of the Code.

Based on the material presented, Sanofi-Aventis therefore believed that the instructions to representatives, their training and briefing, complied with the letter and spirit of the Code and in particular that there had been no breach of Clauses 15.4, 9.1 or 2.

The complainant alleged that the targets referred to above were being used to identify 'poor performers' who might then be selected as possible candidates for redundancy in the forthcoming sales force reorganisation, and that this was a breach of the Code.

The Code covered training and briefing of representatives and their conduct and Sanofi-Aventis believed that the direction given by the company was consistent with the Code in these respects. However, Sanofi-Aventis did not consider that the Code covered assessment of individuals' performance, and therefore submitted that there was no prima facie case to answer on this point.

Furthermore, the need to restructure Sanofi-Aventis' UK sales force was announced at a sales meeting in September. When this complaint was made details of this restructure, including selection procedures and criteria, had not been shared with sales managers or representatives. Sales management was therefore not in a position to inform representatives that levels of bonus might be linked to performance or selection of candidates. The complainant's allegations were therefore based only on conjecture.

PANEL RULING

The Panel noted that the representatives' briefing material and training slides clearly detailed the requirements of Clause 15.4 of the Code and its supplementary information ie that the number of calls made by a representative each year should not normally exceed three on average. This did not include attendance at group meetings, including audiovisual presentations, a visit requested by a doctor or other prescribers, a call made in response to a specific enquiry or a visit to follow up a report of an adverse reaction. The Panel thus noted that, although a representative might call on a doctor or prescriber three times a year the number of contacts with that health professional in the year might be more than that.

The representatives' briefing material about their incentive scheme referred to activity payments which were based on cumulative targeted activity over a 12 month period. All contacts, face-to-face and all types of meeting contributed to this element. Each time activity payments were referred to representatives were reminded of the requirements of Clause 15.4 of the Code.

A presentation about the incentive scheme contained a slide specifically noting the requirements of Clause 15.4. The title of the slide indicated that its inclusion its the presentation was mandatory. The slides about targeted activity payments stated that the targets cited referred to all contacts, by the entire team for a specific customer; they were not individual target call rates.

On the basis of the material before it the Panel considered that there was no evidence to show that Sanofi-Aventis had set its representatives contact target call rates outwith the requirements of the Code no breach of Clause 15.4 was ruled. It thus followed that there was also no breach of Clauses 9.1 and 2 of the Code.

Complaint received	**1 October 2007**
Case completed	**24 October 2007**

CASE AUTH/2055/10/07

VOLUNTARY ADMISSION BY UCB PHARMA

Promotion of prescription only medicine to the public

UCB Pharma stated that, with regret, it brought to the Authority's attention an advertisement placed in a Parkinson's Disease supplement distributed in The Times in September which referred to Keppra (levetiracetam) and Neupro (rotigotine), both prescription only medicines. This breach of the Code was brought to UCB's attention by GlaxoSmithKline.

UCB explained that in early August 2007 its media relations department was invited to contribute to the Parkinson's Disease supplement at issue. At this time, UCB was in the late stages of acquiring Schwarz Pharma which manufactured Neupro for the treatment of Parkinson's Disease. The enquiry and draft copy was hence referred to a brand manager in Schwarz.

The article copy and layout was amended through interactions with various departments. The article was released to the media agency without approval/certification in late August containing two brand names, Keppra and Neupro.

UCB explained that the copy was reviewed outside the approvals process by corporate, commercial and medical departments. Consistently the draft article was assumed to be a corporate press release and as such the opportunity to identify a potential breach was not identified.

Whilst it was intended that the article would raise the profile of the new company, UCB acknowledged that the effect might be considered promotional and as such represented a breach of the Code.

Whilst it did not lessen the nature of this breach, it was significant that the preparation of the advertisement immediately preceded the merger of the two organisations. The brand manager operated without direct supervision and failed to comply with relevant compliance guidelines.

To address the issues identified UCB had undertaken a number of actions. A new standard operating procedure (SOP) relating to media enquiries had been introduced. All media relations, marketing and medical employees would be trained on the new SOP. All Schwarz employees would undergo compliance training in accordance with UCB SOPs. Investigations under the UCB disciplinary procedure were being carried out.

This episode was deeply regrettable and UCB assured the Authority that it took its obligations to the Code very seriously and with utmost importance and would comply fully with the complaints procedure. Recognising that the organisation was going through a period of transformation UCB had done much in the last year to ensure that compliance was at the heart of its culture - details of actions were provided.

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.

The Panel noted that The Times supplement on Parkinson's Disease contained an advertisement placed by UCB. The advertisement, written in the style of an advertorial, stated, *inter alia*, 'With UCB's expertise in CNS, and a market-leading anti-epileptic drug (Keppra), the combination with Schwarz has brought additional strength to UCB's neurology franchise which now includes Neupro, a transdermal patch for the treatment of Parkinson's disease. The patch was launched in the UK in April 2006'.

The Panel examined the emails and other materials provided by UCB and considered that there was a serious lack of understanding throughout the organisation as to the requirements of the Code particularly with regard to relations with the general public and the media. The draft copy for the advertisement was supplied by UCB media relations department which at the outset, despite acknowledging that the intended article was to appear in The Times, queried whether the suggested wording would be acceptable under the Code. The brand manager to whom the draft copy was sent gave his interpretation of what the Code allowed but stated that presumably the article would need to be signed off by corporate affairs and 'both of our medics' (presumably from UCB and Schwarz). The emails sent in July when the project was first discussed were headed 'Advertising proposal – 'Parkinson's Disease' supplement – The Times'. This became 'draft PD article', 'UBC [sic] Advertorial – first proof' and 'UCB Article the Times' in emails sent in August. In that regard the Panel considered that it should have been obvious that it was not draft text for a corporate press release.

The Panel noted that despite the requirements of the Code being queried several times with regard to the advertisement, each time the brand manager stated that he thought it was acceptable under the Code. No-one within the organisation, however, appeared to be prepared to confirm the brand manager's beliefs or challenge them. This demonstrated very poor control

and/or knowledge of the Code. The Panel noted UCB's submission that the brand manager had not complied with company SOPs. The brand manager however, had not acted in isolation. The material had been drafted by the media relations department and seen by the brand manager and members of the medical department. Some members of staff were away when the material was finalised. It was also seen by the managing director. UCB had been badly let down by several members of staff.

The advertisement was signed off on a Schwarz promotional material approval form. The Panel noted UCB's submission that the reviewers of the text were not told by the brand manager that payment was being made for the text to be included in The Times supplement. The Panel noted, however, that the copy approval form described the material as 'Draft article for Times PD [Parkinson's Disease] supplement', the product was 'Neupro' and the audience was 'Times readers'. In that regard the Panel considered that there was enough on the form to ring alarm bells for those reviewing the material. The form had been signed by a product manager and a member of the medical team. The Panel noted UCB's submission that 'incorrect assumptions were made in relation to [the material's] intended purpose'. This was unacceptable; no-one should review material on the basis of assumptions. The Panel considered that the advertisement promoted Keppra and Neupro to the public. 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 had demonstrated a lack of control and poor knowledge of the requirements of the Code throughout the company. High standards had not been maintained. A breach of the Code was ruled. The Panel considered that companies should take particular care when producing material for the public. UCB 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.

UCB Pharma Ltd voluntarily admitted that an advertisement which it placed in a Parkinson's Disease supplement distributed in The Times on 7 September referred to Keppra (levetiracetam) and Neupro (rotigotine), both prescription only medicines.

COMPLAINT

UCB stated that, with regret, it brought to the Authority's attention this advertisement which represented a breach of the Code. The breach was brought to UCB's attention by GlaxoSmithKline. UCB had subsequently investigated the specific circumstances leading to this breach.

UCB explained that in early August 2007, UCB media relations department was invited to contribute to a Parkinson's Disease supplement in the Times. At this time, UCB was in the late stages of acquiring Schwarz Pharma which manufactured Neupro for the treatment of Parkinson's Disease. The enquiry and draft copy was hence referred from UCB media relations to a brand manager in Schwarz on 7 August.

The article copy and layout was amended between 7 and 28 August through interactions with various departments. The article was released to the media agency without approval/certification on 29 August containing two brand names, Keppra and Neupro. Major deficits leading to this breach included the fact that the copy was reviewed outside the approvals process by corporate, commercial and medical departments. Consistently the draft article was assumed to be a corporate press release and as such the opportunity to identify a potential Code breach was not identified.

Whilst it was intended that the article would raise the profile of the new company, UCB acknowledged that the effect might be considered promotional and as such represented a breach of Clause 20.1.

Most significantly the brand manager responsible did not comply with the standard operating procedures (SOPs) and approval processes of either Schwarz or UCB. Specifically the item was released without final approval and certification and as such breached Clause 14.1.

Whilst it did not lessen the nature of this breach, it was significant that the preparation of the advertisement immediately preceded the merger of the two organisations which finally came into effect on 3 September. Notably the brand manager at this time operated without the direct supervision of a line manager. Nonetheless the individual concerned failed to comply with relevant compliance guidelines or with the terms of his contract of employment.

UCB submitted that it had taken the following actions to address the issues identified;

- Introduced a new SOP relating to media enquiries. Specifically this procedure would mandate the initiation of an approvals and certification procedure and origination of a 'job-bag' at the point of entry.
- The training of all media relations, marketing and medical employees on the above.
- All Schwarz employees would undergo compliance training in accordance with UCB SOPs. This programme had already commenced as part of integration training.
- The brand manager responsible for the item was currently being investigated under the UCB disciplinary procedure for breach of the Code and terms and conditions of employment.

Clearly this episode was deeply regrettable and UCB assured the Authority that it took its obligations to the Code very seriously and with utmost importance and would comply fully with the complaints procedure.

Recognising that the organisation was going through a period of transformation UCB had done much in the last year to ensure that compliance was at the heart of its culture - details of actions were provided.

Paragraph 5.4 of 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.

In addition to Clause 20.1 cited by UCB, the company was asked to respond in relation to Clauses 2, 9.1 and 20.2.

RESPONSE

With regard to Clause 20.1, UCB again stressed that the intention behind including the article in the supplement was to highlight the recent merger. UCB never intended to include prescription only medicines in the form of an advertisement to the public, but rather to raise the profile of the newly merged company. Nevertheless, UCB accepted that a section of the final article copy contained text inappropriate given the intended purpose.

With regard to Clause 20.1, the article included the paragraph: 'With UCB's expertise in CNS, a market leading anti-epileptic drug (Keppra), the combination with Schwarz has bought additional strength to UCB's neurology franchise which now includes Neupro, a transdermal patch for the treatment of Parkinson's disease. The patch was launched in the UK in April 2006'. UCB believed that these statements were factually correct, balanced and did not in themselves mislead. The statements did not include any medicinal claims or prejudice patient safety, they also were not made with the specific purpose of encouraging members of the public to ask their health professional to prescribe a specific prescription only medicine. Nonetheless UCB understood that this section of the article might have had the unintended consequence of doing so.

With regard to Clause 9.1, UCB had always maintained high standards and had an excellent track record in this area and indeed with the Authority. Compliance was a top priority of UCB as evidenced by the action it had taken in the last year and as set out in the admission and its appendices. The breach identified in this instance had been treated seriously and UCB immediately embarked upon a corrective action plan which included staff training and an ongoing review of SOPs.

UCB accepted that, on this occasion, the relevant brand manager had failed to comply with existing UCB and Schwarz SOPs. However, UCB believed that this was an exceptional case and the relevant employee's conduct was being investigated. Notwithstanding this, UCB had always and continued to uphold and enforce the high standards demanded of the pharmaceutical industry and it believed that this incident, whilst serious, was not of a distasteful or offensive nature which might be the case with other matters which usually fell to be considered under this clause of the Code.

With regard to Clause 2, UCB believed that this case should not bring discredit to or reduce confidence in the pharmaceutical industry. Whilst UCB acknowledged that one of its employees had departed from its high standards, UCB believed that this was exceptional. The company had established a strong compliance culture throughout the organisation and continued to dedicate resources to ensure that the appropriate training, systems and processes were in place to support this culture. A senior medical advisor had been appointed as compliance manager and UCB staff had participated in training events relating to awareness of the Code and an understanding of its provisions.

To summarise, UCB was confident that this transgression represented an isolated incident to be viewed against the background of a merger. UCB remained confident that this situation would not arise again and continued to take steps to develop compliance and staff training as outlined above. Moreover, on notification of the breach by GlaxoSmithKline, UCB acted promptly to identify the circumstances leading to this situation and executed measures that it believed were appropriate to the issues identified. GlaxoSmithKline had been informed of UCB's determination to disclose all findings to the Authority. The subsequent correspondence with GlaxoSmithKline was provided.

Finally with regard to the specific questions asked, UCB paid a media agency for the advertisement and front page corporate banner. The final copy submitted to the media agency was provided.

FURTHER RESPONSE

In response to a request from the Panel for further information UCB stated that its media department received regular unsolicited communications from a media agency. With regard to the Parkinson's Disease supplement, the agency was advised to contact Schwarz as the expertise resided in that organisation at that time.

A subsequent telephone discussion regarding The Times supplement took place between the relevant Schwarz brand manager and the agency. The call was initiated by the agency which then followed up its conversation by email to the brand manager. A copy of the original email and acceptance of the agency's offer was provided.

The brand manager then contacted the UCB media relations department as he considered that the contribution to the supplement should be written in the context of the impending integration of UCB and Schwarz. The email correspondence between UCB and Schwarz was provided.

The supplement was produced by the agency and

distributed in The Times. As such, there was no contact directly between UCB and The Times during this process.

The 'draft copy' referred to in the admission was draft text for a corporate press release relating initially to the UCB organisation. This was suggested by the UCB media relations department following the referral from the brand manager mentioned above. The 'draft copy' was then referred back to the brand manager for review and confirmation of information relating to Parkinson's Disease and Neupro.

The project was led by the brand manager because Schwarz and UCB were operating as separate organisations at the time and the supplement related to Parkinson's Disease, Schwarz's main therapeutic focus. A job bag was then initiated within Schwarz. The initial text drafted by UCB and the further versions after comment on the information relating to Parkinson's Disease and Neupro were provided.

In the review process the copy was commented upon by several departments between 7 and 28 August. In UCB the copy was reviewed outside a formal approval process and as a result incorrect assumptions were made in relation to its intended purpose.

The contents of the original job bag were provided. Importantly the brand manager did not tell the reviewers the company was paying for the text to be included in The Times supplement. Indeed, it was clear that the brand manager did not appreciate that paying for the article to be published meant that it should be treated as an advertisement rather than a press release. UCB believed that this was not intentional but accepted that reviewers did not identify the risk of potential breach.

The article together with the front page banner were paid for as mentioned in previous correspondence. In UCB's initial response, it referred to the 'advertisement'. This reference represented UCB's agreement that, on review of the actual published supplement, what was actually published was, in reality, an advertisement. However, as mentioned above, throughout the copy review process UCB reviewed the copy as a corporate press release and did not intentionally release it as an advertisement.

The copy was issued to the media agency initially as a text document. The agency converted this into a PDF and returned it to UCB; a copy was provided. This PDF was reviewed internally with further comments made. The amended document was then returned to the agency without further internal approval as required in the Schwarz approval process.

The brand manager from Schwarz arranged for both items to be released to the agency. As previously discussed the item was released without completion of the job bag and without certification.

According to Clause 14.3 of the Code, a press release should be examined to ensure that it did not contravene the Code or the relevant statutory requirements. UCB and Schwarz policy was to review and certify all press releases. The brand manager acted against the existing Schwarz SOP at the time. As a result of this unfortunate and unforeseen event, UCB had updated its 'Relationship with the Media and Public SOP' and in future would be certifying all communications external to UCB. A copy of this SOP was provided.

PANEL RULING

The Panel noted that the supplement on Parkinson's Disease, distributed with The Times, 7 September 2007, contained an advertisement placed by UCB. The advertisement, written in the style of an advertorial, stated, *inter alia*, 'With UCB's expertise in CNS, and a market-leading anti-epileptic drug (Keppra), the combination with Schwarz has brought additional strength to UCB's neurology franchise which now includes Neupro, a transdermal patch for the treatment of Parkinson's disease. The patch was launched in the UK in April 2006'.

The Panel examined the emails and other materials provided by UCB and considered that there was a serious lack of understanding throughout the organisation as to the requirements of the Code particularly with regard to relations with the general public and the media (Clause 20). The draft copy for the advertisement was supplied by UCB media relations department which at the outset, despite acknowledging that the intended article was to appear in The Times, queried whether the suggested wording would be acceptable under the Code. The brand manager to whom the draft copy was sent gave his interpretation of what the Code allowed but stated that presumably the article would need to be signed off by corporate affairs and 'both of our medics' (presumably from UCB and Schwarz). The emails sent in July when the project was first discussed were headed 'Advertising proposal – 'Parkinson's Disease' supplement – The Times'. This became 'draft PD article', 'UBC [sic] Advertorial – first proof' and 'UCB Article the Times' in emails sent in August. In that regard the Panel considered that it should have been obvious that it was not draft text for a corporate press release.

The Panel noted that despite the requirements of the Code being queried several times with regard to the advertisement, each time the brand manager stated that he thought it was acceptable under the Code. No-one within the organisation, however, appeared to be prepared to confirm the brand manager's beliefs or challenge them. This demonstrated very poor control and/or knowledge of the Code. The Panel noted UCB's submission that the brand manager had not complied with company SOPs. The brand manager however, had not acted in isolation. The material had been drafted by the media relations department and seen by the brand manager and members of the medical department. Some members of staff were away when the material was finalised. It was also seen by the managing director. UCB had been badly let down by several members of staff.

The advertisement was signed off on a Schwarz

promotional material approval form. The Panel noted UCB's submission that the reviewers of the text were not told by the brand manager that payment was being made for the text to be included in The Times supplement. The Panel noted, however, that the copy approval form described the material as 'Draft article for Times PD [Parkinson's Disease] supplement', the product was 'Neupro' and the audience was 'Times readers'. In that regard the Panel considered that there was enough on the form to ring alarm bells for those reviewing the material. The form had been signed by a product manager and a member of the medical team. The Panel noted UCB's submission that 'incorrect assumptions were made in relation to [the material's] intended purpose'. This was unacceptable; no-one should review material on the basis of assumptions. The Panel considered that the advertisement promoted Keppra and Neupro to the public. 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 had demonstrated a lack of control and poor knowledge of the requirements of the Code throughout the company. 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. UCB 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 8 October 2007

Case completed 3 December 2007

CASE AUTH/2056/10/07

LILLY v NOVO NORDISK

Levemir journal advertisement

Lilly alleged that the artwork in a Novo Nordisk advertisement for Levemir (insulin detemir) in Diabetes Update, Autumn 2007, was misleading and ambiguous in that the picture of five overweight adult bodies in a swimming pool in conjunction with the strapline 'Levemir is Changing Figures', implied that Levemir was associated with weight loss.

Weight gain was a recognised side-effect of insulin therapy and while Levemir caused less weight gain compared with other insulins (Levemir summary of product characteristics (SPC)) there was no evidence to substantiate weight loss. The SPC stated that in type 2 diabetes, Levemir treated patients had been shown to gain 0.7-3.7kg, depending on the dosing regime. Lilly agreed that the artwork represented typical patients with type 2 diabetes but the proximity of the 'changing figures' strapline meant that the emphasis became that of weight loss.

The Panel noted that the advertisement featured an underwater photograph of five overweight women treading water in a swimming pool. Only their bodies from the neck down could be seen. Beneath the photograph was the prominent claim 'Levemir is changing figures'. In the Panel's view the implication was that Levemir would change the women's figures for the better ie they would lose weight. Although boxed text contained the claim 'Less weight gain than NPH and insulin glargine' this did not negate the otherwise misleading impression given by the photograph and claim. The Panel considered that the advertisement was misleading as alleged. Breaches of the Code were ruled which were upheld on appeal by Novo Nordisk with the Appeal Board further considering that the prominent claim 'Levemir is changing figures' was a play on words and, in conjunction with the photograph, implied that Levemir would change the women's figures for the better ie they would lose weight and their shape would change. 'Figures' was much more likely to be thought of in terms of ladies' figures rather than clinical values such as HbA1c etc as submitted by Novo Nordisk.

Eli Lilly and Company Limited complained about an advertisement (ref UK/LM/0707/0052) for Levemir (insulin detemir) placed by Novo Nordisk Limited in Diabetes Update, Autumn 2007. Lilly supplied a number of insulins.

COMPLAINT

Lilly alleged that the artwork (five overweight adult bodies in a swimming pool) in conjunction with the strapline 'Levemir is Changing Figures' was misleading; it implied that Levemir was associated with weight loss.

Weight gain was a recognised side-effect of insulin therapy and while Levemir had been proven to cause less weight gain compared with other insulins (Levemir summary of product characteristics (SPC)) there was no evidence to substantiate weight loss in the SPC or the references cited. In addition, the SPC clearly showed that in studies of patients with type 2 diabetes, Levemir caused a weight gain ranging from 0.7-3.7kg, depending on the dosing regime.

Novo Nordisk argued that the artwork used represented typical patients with type 2 diabetes; and while Lilly agreed this was true, the proximity of the artwork to the 'changing figures' strapline meant that the emphasis to the reader became that of weight loss with this treatment.

Lilly alleged that the advertisement was ambiguous and in breach of Clauses 7.2 and 7.8 of the Code.

RESPONSE

Novo Nordisk stated that Lilly had failed to realise that the tagline clearly referred to the key findings from two randomized clinical trials conducted by Novo Nordisk (Philis-Tsimikas *et al*, 2006, and Rosenstock *et al*, 2006) in which the numerical values for the following figures were consistently and significantly changed:

- **Effective once-daily HbA1c control**

(HbA1c improvement with Levemir is -1.48%, Philis-Tsimikas el al)

- **Less weight gain compared to NPH and insulin glargine**

(weight gain with Levemir 0.7kg, Philis-Tsimikas *et al*)

(weight gain with Levemir 3kg, Rosenstock *et al*)

- **A low risk of nocturnal hypoglycaemia compared with NPH**

(53% risk reduction (24-hour rate) compared to NPH, Philis-Tsimikas *et al*)

(65% risk reduction (nocturnal) compared to NPH, Philis-Tsimikas *et al*)

These claims about the complex, multifactorial management of diabetes could be substantiated by the above mentioned studies. The weight benefit of Levemir as compared to other basal insulins had also been recognized by the European Medicines Evaluation Agency (EMEA) and Levemir had this statement in its SPC 'Studies in patients with type 2 diabetes treated with basal insulin in combination with oral antidiabetic drugs demonstrates that glycaemic control (HbA1c) with Levemir is comparable to NPH insulin and insulin glargine and associated with less weight gain'. Novo Nordisk had

never claimed that Levemir would result in weight loss in patients with type 2 diabetes.

Novo Nordisk believed that its letter to Lilly of 24 September provided adequate response to this issue and asked that that letter form part of its substantive response.

Novo Nordisk agreed that the picture was of overweight women. However, almost 80% of patients with type 2 diabetes were overweight and of these more than one third were obese (Ridderstrale *et al*, 2006). Thus this picture represented typical patients with type 2 diabetes. Since the licensed indication of Levemir was the treatment of diabetes mellitus, Novo Nordisk could hardly see any other option than using a picture of typical type 2 diabetic patients when advertising the product in this type of diabetes. Using a picture of patients with normal weight when the advertisement was about type 2 diabetes would be rather atypical. The picture itself did not imply weight loss, but highlighted the complex treatment approach type 2 diabetics needed.

Novo Nordisk submitted that using photographs of obese people when promoting a medicine for the treatment of type 2 diabetes was acceptable under the Code and specifically Clause 7.8. Novo Nordisk therefore believed this artwork was not in breach of Clause 7.8.

PANEL RULING

The Panel noted that the advertisement featured an underwater photograph of five overweight women treading water in a swimming pool. Only their bodies from the neck down could be seen. Beneath the photograph was the prominent claim 'Levemir is changing figures'. In the Panel's view the implication was that Levemir would change the women's figures for the better ie they would lose weight. Although boxed text contained the claim 'Less weight gain than NPH and insulin glargine' this did not negate the otherwise misleading impression given by the photograph and claim. The Panel considered that the advertisement was misleading as alleged. Breaches of Clauses 7.2 and 7.8 of the Code were ruled.

APPEAL BY NOVO NORDISK

Novo Nordisk submitted that there were two claims equally close to the artwork. The first one 'Now approved: Once-daily Levemir + [oral antidiabetic] OADs therapy' clearly set the scene. The advertisement was about the benefits of the most popular form of insulin initiation in type 2 diabetes ie basal insulin plus OAD(s). There was no reason to believe that anyone treating type 2 diabetics would not know that insulin initiation was traditionally associated with weight gain (Yki-Jarvinen *et al* 1997). The only reason to introduce insulin to OAD therapy in type 2 diabetes was to improve glycaemic control, as measured by HbA1C. It was clear that the primary figure that Levemir was changing did not relate to weight but to the improvement/reduction in HbA1C figure. This aspect was adequately clarified in the boxed text where the three claims were referenced by the results of Philis-Tsimikas *et al*, Rosenstock *et al*, 2006 and the Levemir SPC. The claim 'Levemir is changing figures' was also referenced to Philis-Tsimikas *et al* in which the results showed an improvement in: the level of HbA1C (-1.48% reduction from baseline), the risk of hypoglycaemia when compared to NPH insulin (53% risk reduction of 24-hour events and 65% risk reduction of nocturnal events) and the magnitude of treatment associated weight gain compared to NPH insulin (0.9kg (56%) less weight gain after insulin initiation).

Novo Nordisk submitted that inevitably the treatment of diabetes required a complex multifactorial management of several clinical parameters (primarily glycaemic control) in order to prevent/delay late complications (eg diabetic eye and kidney disease). This complex, stepwise approach was widely recognized, followed and applied at all stages of this progressive metabolic disorder. Physicians were well aware of the importance of addressing glycaemic control along side reducing the risk of hypoglycaemic events and weight gain together. Therefore it was clear to the reader that 'changing figures' in relation to the use of insulin directly impacted and could only relate to HbA1C, hypoglycaemia and weight gain.

On the basis of the above Novo Nordisk submitted that the claim did not mislead by implying that use of Levemir would result in weight loss; as such the claim was not in breach of Clause 7.2.

Novo Nordisk noted the Panel also ruled a breach of Clause 7.8 as the artwork was considered to be misleading as showing five overweight women and implying that the use of Levemir would result in weight loss. As defined clearly by the heading, the advertisement was about an insulin treatment for type 2 diabetes. Nobody could argue that a typical patient with type 2 diabetes was overweight/obese, as accepted by Lilly. Therefore to use an image that did not reflect the characteristics of a type 2 diabetic would be inappropriate. In the circumstances, there appeared no other option than to use an image that portrayed the typical characteristics of this disease. For these reasons, Novo Nordisk submitted that this artwork was not in breach of Clause 7.8.

COMMENTS FROM LILLY

Lilly noted, Novo Nordisk's submission that the context of the advertisement was set out in two claims equally close to the artwork. However, it failed to comment that 'Levemir is changing figures' was at least twice the size and thus of far greater prominence than the other claim. It was clearly positioned in the centre of the advertisement for maximum effect.

Lilly noted that weight gain was a recognised side effect of insulin therapy. Despite this, the impression given by the claim and artwork was that Levemir was associated with weight loss. While Levemir caused less weight gain compared with other insulins (Levemir SPC) there was no evidence to substantiate weight loss in the SPC or references given. The

Levemir SPC clearly stated that in studies of patients with type 2 diabetes, Levemir caused a weight gain ranging from 0.7-3.7kg, depending on the dosing regime.

Lilly noted that in Novo Nordisk's response, it commented on the 'weight benefit' associated with Levemir relative to insulin glargine. However, Lilly alleged that any weight gain could only be seen as a disadvantage in a condition such as type 2 diabetes where, as accepted by Novo Nordisk, 80% of the patients were overweight and of these more than one third obese (Ridderstrale *et al*). Lilly reiterated that the common interpretation of 'weight benefit', particularly in patients with diabetes, would be of weight loss.

Regarding the choice of artwork, Lilly considered that there were many alternatives to describe a typical type 2 diabetic other than overweight swimmers.

Lilly alleged that both the picture and claim were chosen with the precise purpose of introducing ambiguity and implying that Levemir had 'benefits', specifically weight loss, which could not be substantiated.

APPEAL BOARD RULING

The Appeal Board noted that the advertisement featured an underwater photograph of five overweight women treading water in a swimming pool. Only their bodies from the neck down could be seen. Beneath the photograph was the prominent claim 'Levemir is changing figures'. In the Appeal Board's view the claim was a play on words and, in conjunction with the photograph, implied that Levemir would change the women's figures for the better ie they would lose weight and their shape would change. 'Figures' was much more likely to be thought of in terms of ladies figures rather than clinical values such as HbA1c etc. Although boxed text contained the claim 'Less weight gain than NPH and insulin glargine' this did not negate the otherwise misleading impression given. The Appeal Board considered that the advertisement was ambiguous and upheld the Panel's ruling of breaches of Clauses 7.2 and 7.8 of the Code. The appeal was unsuccessful.

Complaint received 10 October 2007

Case completed 7 January 2008

CASE AUTH/2057/10/07

GLAXOSMITHKLINE v GILEAD SCIENCES

Promotion of Truvada

GlaxoSmithKline complained about the promotion of Truvada (emtricitabine and tenofovir) by Gilead. The items at issue were two leavepieces, one describing the safety outcomes and the other describing the efficacy outcomes of the BICOMBO study. GlaxoSmithKline supplied Kivexa (abacavir and lamivudine).

GlaxoSmithKline explained that Kivexa and Truvada were both dual nucleoside backbones formulated as fixed dose combinations, licensed for the treatment of HIV infection. Currently there were no data available from robust, double blind, head-to-head studies directly comparing the efficacy and tolerability of Kivexa and Truvada, but studies were ongoing.

BICOMBO was an investigator sponsored, collaborative study jointly funded by GlaxoSmithKline and Gilead. In this open-label study, patients on a stable lamivudine-containing regimen were randomised to switch their nucleoside reverse transcriptase inhibitor (NRTI) backbone to either Truvada or Kivexa, whilst keeping the third agent of the regimen unchanged. The primary study endpoint was the proportion of patients with treatment failure for any reason through 48 weeks and was powered for non-inferiority with an upper limit of 95% confidence interval of estimated difference < 12.5%.

Secondary endpoints included the proportion of patients with virological failure at or before 48 weeks, CD4 changes and changes in fasting plasma lipids, body fat, bone mineral density and renal function. The 48 week data from this study were presented at an international conference in July 2007. The study concluded that for the primary parameter of treatment efficacy, the Kivexa group did not meet the non-inferiority endpoint compared with the Truvada group. For the secondary parameter of virologic efficacy, Kivexa met non-inferiority criteria compared to Truvada.

GlaxoSmithKline noted in particular the following three claims in the efficacy outcomes leavepiece:

- **'For virologic efficacy, Kivexa met non-inferiority criteria compared to Truvada; however, there were more failures with Kivexa (2.4%) than Truvada (0%)'**
- **'Treatment failure rates for Kivexa were 6% higher than Truvada'**
- **'For treatment efficacy, Kivexa did not meet the non-inferiority endpoint compared to Truvada'.**

These claims of superiority, based on virological failures, were made despite the two therapies being statistically non-inferior for virological efficacy. This, with the lack of non-inferiority being proven for treatment failures as the primary parameter, was misleading as the study was not powered as a superiority study. GlaxoSmithKline alleged that these three claims were collectively in breach of the Code.

Additionally, given that there was a difference in the baseline regimens of the two groups, the randomisation had generated an inherent bias. More patients in the Truvada arm were on a tenofovir-containing regimen at baseline (34%) than patients continuing on an abacavir-containing regimen (7%) in the Kivexa arm. As such there would be an element of patients 'surviving' on existing therapy causing this bias as different proportions of patients in each arm had a therapy change.

The impression of superiority given by the bar chart should be corrected by explicitly stating the correct statistical interpretation as per the study design.

GlaxoSmithKline further noted that baseline resistance testing was not performed in this study and this could have affected the virologic endpoint. The authors reported that the 4 patients experiencing failure in the Kivexa arm had previously received 2 or more regimens for 1-5 years. Whilst they reported that these patients had not previously received abacavir, a number of NRTI-associated mutations could confer cross resistance to abacavir.

GlaxoSmithKline stated that baseline resistance testing would have allowed interpretation of these results, and stratification in the randomisation based upon this would have controlled for this factor. Because this was not done, no claim should be made on virological efficacy or failure rates without putting these facts in context. GlaxoSmithKline alleged that the claims were in breach of the Code for these reasons also and should not be made without an explicit qualification of this source of bias.

The issue was whether the virological failures emerged following therapy switch or were present prior to study commencement. Without this data, it was difficult to understand the clinical relevance of the virological failure. Any claims should reflect this uncertainty.

GlaxoSmithKline noted that the efficacy outcomes leavepiece also contained the wording 'Retrospective HLA-B5701 testing showed of 9 suspected HSR [hypersensitivity reactions] in the Kivexa arm, only 3 were HLA +ve. Clinical vigilance for HSR is essential during treatment' which implied that HLA-B*5701 screening was not an effective tool to reduce the

incidence of abacavir hypersensitivity and that if these subjects had been prospectively screened, then only three HSRs would have been prevented and the other six would still have occurred. This was extremely misleading in the light of all the available evidence and only referred to clinically-suspected HSRs rather than the more robust measure of immunologically-confirmed HSR.

When prospective screening was used, the diagnosis rate of HSR had been shown to reduce significantly if a clinician knew that a patient was HLA-B*5701 negative (Rauch *et al*). Indeed, in PREDICT-1 only 3.4% vs 7.8% of patients were diagnosed with a clinically-suspected HSR in the prospective screening arm vs the control arm. None of these subjects went on to have an immunologicially-confirmed HSR indicating that the majority of these diagnoses were misdiagnoses and not true HSR (Mallal *et al*, 2007).

Although factually correct, the statement could easily be misinterpreted as meaning that two-thirds of Kivexa HSR cases were in patients who did not possess the HLA-B*5701 allele. This ambiguity was due to the open-label design meaning that only patients in the Kivexa arm would have been suspected of being at risk of HSR and thus diagnosed as such in response to one or more symptoms raising clinical suspicion. In a blinded study suspected-HSRs could also have been diagnosed in the Truvada arm.

GlaxoSmithKline alleged that the statement at issue was ambiguous and misleading. Additionally the tone of the claim disparaged Kivexa. The statement cast doubt over the robustness of current evidence for the utility of HLA-B*5701 screening from the PREDICT-1 study.

Given the limitations of the BICOMBO study design, GlaxoSmithKline alleged that Gilead's interpretation of the data to support the promotion of Truvada was misleading.

The Panel noted that the BICOMBO study was the first to directly compare the efficacy and safety of Kivexa and Truvada. The study would run for three years but to date data was only available from the first 48 weeks of the study. The study had thus not run its course and there was limited data in the public domain with regard to study design, statistical methods etc. The study was designed to assess the non-inferiority of the two combinations with respect to treatment efficacy (primary endpoint) and virological efficacy (secondary endpoint). Kivexa failed to meet the primary non-inferior endpoint compared with Truvada. The authors suggested that this might have been because some patients had to discontinue Kivexa treatment due to abacavir hypersensitivity reactions (discontinuation of study therapy was regarded as treatment failure). In terms of virological efficacy Kivexa met non-inferiority criteria compared with Truvada however there were more failures with Kivexa than Truvada (2.4% vs 0% respectively).

The Panel noted that the efficacy leavepiece featured a bar chart detailing treatment failure and virological failure. The visual impression of the bar chart was that Truvada was superior to Kivexa although this had not been shown statistically. Although the results favoured Truvada, the study was not powered to show superiority; in any event only 48 week data was available from a study which still had over 2 years to run. The following claims appeared to the right of the bar chart: 'For virologic efficacy, Kivexa met non-inferiority criteria compared to Truvada; however there were more failures with Kivexa (2.4%) than Truvada (0%)'; 'Treatment failure rates with Kivexa were 6% higher than Truvada' and 'For treatment efficacy, Kivexa did not meet the non-inferiority endpoint compared to Truvada.'

The Panel noted that although Kivexa had not been shown to the non-inferior to Truvada in terms of treatment efficacy, Truvada had not been shown to be superior. In terms of virological efficacy Kivexa was shown to be non-inferior to Truvada although there were more treatment failures with Kivexa than Truvada. The Panel considered that although the interim data from the BICOMBO study was of undoubted interest, but noted that the study had yet to run its full course. The Panel considered that the efficacy outcomes leavepiece implied that Truvada had been shown to be superior compared with Kivexa which was not so. The Panel considered that the claims detailed above were misleading as alleged. Breaches of the Code were ruled.

The Panel noted that the leavepiece at issue did not record the fact that no baseline resistance testing had taken place although it did state that at baseline patients had been virologically suppressed for at least 6 months. The definition of suppression (<200 copies HIV RNA per ml) was not stated although virological failure was stated to be ≥200 copies/ml. The Panel noted Gilead's submission that baseline resistance testing could not have been performed at study entry due to the viral load being undetectable.

Overall the Panel considered that whilst it might have been helpful for readers to know that baseline testing had not been carried out, the omission of such data was not misleading per se. Readers were told that patients were virologically suppressed at baseline. On balance the Panel considered that the claims 'For virological efficacy, Kivexa met non-inferiority criteria compared to Truvada; however there were more failures with Kinvexa (24%) than Truvada (0%)' and 'For treatment efficacy, Kivexa did not meet the non-inferiority endpoint compared to Truvada' were not misleading on this point and ruled no breach of the Code.

The Panel considered that the claim 'Retrospective HLA-B5701 testing showed of 9 suspected HSR in the Kivexa arm, only 3 were HLA positive. Clinical vigilance for HSR is essential during treatment' clearly referred to suspected HSR and not immunologically-confirmed HSR. The Panel noted that the claim implied that 6 cases of suspected HSR were in patients who were HLA negative. Section 4.4 of the Kivexa SPC referred to the possibility of suspected HSR in

patients who did not carry HLA-B*5701. The Panel did not consider the claim at issue was misleading, ambiguous or incapable of substantiation nor did it disparage Kivexa. No breaches of the Code were ruled.

Although noting its comments above the Panel did not consider that high standards had not been maintained. No breach of the Code was ruled.

With regard to the safety outcomes leavepiece, GlaxoSmithKline noted the following:

'Switching virologically suppressed patients to Truvada provides a significantly more favourable lipid profile* than Kivexa, with no differences in renal function or bone mineral density'. (The asterisk referred to TG, TC and LDL and was shown as a footnote.)

GlaxoSmithKline had alleged that it was misleading to claim that Truvada had a significantly better lipid profile than Kivexa based on only three of the four parameters measured, as the fourth (HDL) was widely believed to be an important factor when evaluating cardiovascular risk, as in the Framingham calculator and the British Heart Foundation guidelines. Triglycerides were understood to play a minor role.

Furthermore GlaxoSmithKline alleged that the claim 'Switching to Truvada provides a significantly more favourable lipid profile than Kivexa' was misleading with regard to the safety of Truvada. The Truvada summary of product characteristics (SPC) listed hypertriglyceridaemia as a commonly reported adverse event, and cautions regarding hypercholesterolaemia in combination antiretroviral therapy in section 4.8 (with reference to section 4.4). This was likely to be in breach of the Code by not encouraging the rational use of the medicine.

Finally, GlaxoSmithKline alleged that the safety outcomes leavepiece was misleading in that it did not mention the primary outcomes of the study. This was not a safety study. Secondary parameter claims could not be made without presenting the primary parameter data from the study to allow clinicians to assess the relative efficacy and safety of the two components. Gilead's assertion that the primary efficacy parameters were presented elsewhere (ie in a separate leavepiece) did not allay GlaxoSmithKline's concerns, as it considered that each piece must be capable of standing alone.

The Panel noted that although Gilead had agreed to refer to all four lipid results (TG, TC, LDL and HDL) in its claims regarding lipid profile, it had not agreed to modify the claim 'Switching virologically suppressed patients to Truvada provides a significantly more favourable lipid profile …'. The results shown to substantiate this claim were the absolute changes in lipid levels over 48 weeks and the lack of change in the TC/HDL ratio over the same time period. However, although, for instance, readers were told that LDL rose by 7mg/dL over 48 weeks there was no indication as to the clinical significance. The Panel considered that the information given was such that prescribers would be unable to form their own opinion as to the clinical significance of the results; the leavepiece was thus misleading in this regard. A breach of the Code was ruled.

The Panel noted that the leavepiece depicted a decrease in triglycerides (-16mg/dL) over 48 weeks. The Truvada SPC, however, listed hypertriglyceridaemia as a common side-effect. The Panel considered that it was misleading to refer to the observed decrease in triglycerides without noting the statement in the SPC regarding hypertriglyceridaemia. A breach of the Code was ruled.

The Panel did not consider that it was necessarily unacceptable to produce a leavepiece focussing only on the safety data when such data had come from secondary endpoints of a study. None of the primary end-points were safety-related and so in that regard the safety data was capable of standing alone. However the leavepiece at issue did not make it clear that the data presented was from secondary endpoints and that primary endpoints had related to efficacy. Some readers might assume that the BICOMBO study was primarily a safety study which was not so. The leavepiece was misleading in this regard. Breaches of the Code were ruled.

GlaxoSmithKline UK Ltd complained about the promotion of Truvada (emtricitabine and tenofovir) by Gilead Sciences Limited. The items at issue were two leavepieces: describing the safety outcomes (ref 164/UKM/07-08/CM/510) and efficacy outcomes (ref 164/UKM/07-08/CM/505) of the BICOMBO study. GlaxoSmithKline supplied Kivexa (abacavir and lamivudine). There had been inter-company dialogue but agreement had not been reached on most of the issues.

GlaxoSmithKline explained that Kivexa and Truvada were both dual nucleoside backbones formulated as fixed dose combinations, licensed for the treatment of HIV infection and recommended in the BHIVA (British HIV Association) guidelines. Currently there were no data available from robust, double blind, head-to-head studies directly comparing the efficacy and tolerability of Kivexa and Truvada, but such studies were ongoing.

BICOMBO was an investigator sponsored, collaborative study jointly funded by GlaxoSmithKline and Gilead. In this open-label study, patients on a stable lamivudine-containing regimen were randomised to switch their nucleoside reverse transcriptase inhibitor (NRTI) backbone to either Truvada or Kivexa, whilst keeping the third agent of the regimen unchanged. The primary study endpoint was the proportion of patients with treatment failure for any reason through 48 weeks and was powered for non-inferiority with an upper limit of 95% confidence interval (CI) of estimated difference < 12.5%.

Secondary endpoints included the proportion of patients with virological failure at or before 48 weeks, CD4 changes and changes in fasting plasma lipids, body fat, bone mineral density and renal function. The 48 week data from this study were presented at the

International AIDS Society (IAS) conference in Sydney, July 2007. The study concluded that for the primary parameter of treatment efficacy, the Kivexa group did not meet the non-inferiority endpoint compared with the Truvada group. For the secondary parameter of virologic efficacy, Kivexa met non-inferiority criteria compared to Truvada.

On 24 August, GlaxoSmithKline contacted Gilead about claims in the leavepiece; Study highlights: BICOMBO – safety outcomes. GlaxoSmithKline's initial concerns related to selective reference to lipid parameters that improved on Truvada (triglycerides (TG), total cholesterol (TC), low density lipoprotein (LDL)), whilst ignoring the negative impact on high density lipoprotein (HDL). Additionally Gilead selectively ignored the neutral impact of Kivexa on HDL which was significantly different to that seen on Truvada.

GlaxoSmithKline noted Gilead's treatment of some non statistically significant differences in the piece whereby it claimed that there were no differences between the two treatment arms as regards changes in renal function, bone mineral density and limb fat. The small differences seen in favour of Kivexa failed to reach statistical significance. This contrasted with Gilead's treatment of other non statistically significant differences where the trend favoured Truvada.

GlaxoSmithKline also noted that flaws in the design of the BICOMBO study meant that the claims were not justified.

GlaxoSmithKline stated that Gilead considered that its presentation of the results from the BICOMBO study in the leavepiece at issue accurately reflected the study authors' conclusions. However, given that the fundamental principle of the Code when using a study to promote a product was that the claims must represent the balance of evidence available as well as being supportable by robust data, GlaxoSmithKline alleged that the leavepiece were misleading due to over interpretation and selective reporting of the study endpoints. There were additionally a number of design flaws in the BICOMBO study which cast doubt over the interpretation of the results and therefore the strength and nature of claims that could be made when using the data promotionally.

These flaws included: bias in randomisation, absence of baseline resistance testing, selective reporting of lipid endpoints, underpowered sub-analysis of other metabolic endpoints, retrospective HLA-B*5701 screening and open-label study design.

1 Leavepiece entitled 'Study hightlights: BICOMBO – efficacy outcomes'.

COMPLAINT

Bias in randomisation

GlaxoSmithKline stated in its initial letter, 24 August, about the safety outcomes leavepiece, that 'Additionally, we wish to point out that 34% of the patients assigned to the Truvada arm, were already taking tenofovir at baseline and hence had been controlled and tolerating tenofovir for 6 months. In contrast only 7% of patients assigned to the Kivexa arm were already on abacavir at baseline. Therefore, when using this data, it is important that you point out that the data will be skewed by inclusion of these patients.' and '… With no baseline resistance tests, 2 or more previous [antiretroviral therapy] regimens, small group numbers, and mismatched baseline [antiretroviral therapy] (17% on abacavir vs 34% on tenofovir in [the Truvada] arm), it is imperative that messages being used by your [representatives] do take account of all the facts, and accurately reflect the data'.

Gilead replied as follows: 'The only key message we are using is that contained within the box at the bottom of the Study Highlights: BiCombo Efficacy outcomes [leavepiece]. This states that 'switching to Truvada in virologically suppressed patients provides continued treatment efficacy with 0% virological failures over 48 weeks' and makes no reference to a switch to Kivexa'.

However, the efficacy outcomes leavepiece made three claims related to comparative data that could be seen to encourage switching in the bullet points on the right-hand side, stating:

- 'For virologic efficacy, Kivexa met non-inferiority criteria compared to Truvada; however, there were more failures with Kivexa (2.4%) than Truvada (0%)'
- 'Treatment failure rates for Kivexa were 6% higher than Truvada'
- 'For treatment efficacy, Kivexa did not meet the non-inferiority endpoint compared to Truvada'.

These claims of superiority, based on virological failures, were made despite the two therapies being statistically non-inferior for virological efficacy. This, with the lack of non-inferiority being proven for treatment failures as the primary parameter, was clearly misleading and in breach of the Code as the study was not powered as a superiority study. GlaxoSmithKline alleged that these three statements were collectively in breach of Clauses 7.2 and 7.3.

Additionally, given that there was a difference in the baseline regimens of the two groups, the randomisation had generated an inherent bias. More patients in the Truvada arm continued on a tenofovir-containing regimen (34%) than patients continuing on abacavir-containing regimen (7%) in the Kivexa arm. As such there would be an element of patients 'surviving' on existing therapy causing this bias as different proportions of patients in each arm had a therapy change.

GlaxoSmithKline requested that Gilead either change its leavepiece to include all of the baseline regimen data, pointing out the above mismatch of 7% vs 34%, or show only the unpowered analysis with the patients receiving baseline abacavir in the Kivexa arm and tenofovir in the Truvada arm removed. This would need to be labelled as under-powered for statistical analysis for clarity. Additionally GlaxoSmithKline insisted that the impression of superiority given by the

bar chart be corrected by explicitly stating the correct statistical interpretation as per the study design in the title of this graphic.

Gilead argued that it considered the claims were acceptable because they were the conclusions of the author. In GlaxoSmithKline's opinion, the fact that these might have been the conclusion of the author did not make them acceptable for use under the Code, as the two therapies were statistically non-inferior for virological efficacy.

When challenged on the point of randomisation bias at the late breaker session where these data were presented, the author presented an additional slide (slide 32 of the IAS presentation) showing an analysis of treatment failures but with all patients receiving baseline tenofovir or abacavir therapy removed. This analysis yielded similar results to the full data set. The decrease in patient numbers however meant that the statistical power was reduced which was likely to have widened the confidence intervals significantly, thus making any numerical treatment difference appear inflated. In this case the confidence intervals ranged from -1.4% to 16.8%, a range of 18.2%; encompassing zero and the non-inferiority margin. Given the lack of statistical rigour, the non- inferiority design and the expanding confidence intervals once the bias was corrected, the superiority claims made by Gilead were not balanced or supported by the evidence available and thus in breach as alleged.

Gilead implied that GlaxoSmithKline's criticism of the study was a criticism of the investigator. This was not so. This was simply a desire to correct misrepresentation of the data by Gilead by ensuring that issues with the study design were made clear to prescribers. As previously mentioned, the bias in the randomization of the study (regardless of the financial arrangements, the study being co-funded by GlaxoSmithKline and Gilead) was a fact that was self-evident based on the lack of baseline therapy stratification. This would inevitably affect the results and their interpretation. As explained above, removal of those patients randomised to continue on tenofovir or abacavir, as shown by the investigator in response to questions at the IAS conference, resulted in an underpowered analysis.

GlaxoSmithKline contrasted the position taken here by Gilead in making such strong claims of superiority based on a non-inferiority design, with its claims (referred to above) made of no difference on other parameters where no statistically significant difference was seen, but trends favoured Kivexa.

Although the BICOMBO study results demonstrated trends towards differences between Truvada and Kivexa as regards renal function and bone mineral density, these failed to reach statistical difference. Consequently GlaxoSmithKline considered that the statement regarding these parameters should read 'no significant differences' rather than 'no differences'. Gilead had agreed to make this amendment when reprinting the leavepieces, but did not define when that would be.

Absence of baseline resistance testing

With regard to the claims in the efficacy outcomes leavepiece:

- 'For virologic efficacy, Kivexa met non-inferiority criteria compared to Truvada; however, there were more failures with Kivexa (2.4%) than Truvada (0%)'
- 'For treatment efficacy, Kivexa did not meet the non-inferiority endpoint compared to Truvada'

Baseline resistance testing was not performed in this study and this could have affected the virologic endpoint. The authors reported that the 4 patients experiencing failure in the Kivexa arm had previously received 2 or more regimens for 1-5 years. Whilst they reported that these patients had not previously received abacavir, a number of NRTI-associated mutations could confer cross resistance to abacavir. Indeed, 2 of the 4 patients had multiple resistance mutations suggestive of possible prior resistance. Another patient had previous virological failure and wild-type virus, suggestive of poor adherence.

GlaxoSmithKline stated that baseline resistance testing would have allowed interpretation of these results, and stratification in the randomisation based upon this would have controlled for this factor. Because this was not done, no claim should be made on virological efficacy or failure rates without putting these facts in context. GlaxoSmithKline alleged that the claims were in breach of Clause 7.2 for these reasons also and should not be made without an explicit qualification of this source of bias.

In its response of 5 October, Gilead asserted that as baseline resistance testing was not the standard of care in the centres carrying out the study it was not included in the study protocol. Gilead assumed that baseline mutation in the Kivexa and Truvada arms would have been similar, but such an assumption could not be made.

GlaxoSmithKline pointed out to Gilead that whether the resistance testing was standard of care or not was irrelevant. The issue was whether the virological failures emerged following therapy switch or were present prior to study commencement. Without this data, it was difficult to understand the clinical relevance of the virological failure. Any claims should reflect this uncertainty. As mentioned above, the fact that the author presented these conclusions at the IAS did not make their use acceptable under the Code.

*Retrospective HLA-B*5701 screening and open-label study design*

The efficacy outcomes leavepiece contained the wording:

- 'Retrospective HLA-B5701 testing showed of 9 suspected HSR [hypersensitivity reactions] in the Kivexa arm, only 3 were HLA +ve. Clinical vigilance for HSR is essential during treatment'.

This statement implied that HLA-B*5701 screening was not an effective tool to reduce the incidence of abacavir hypersensitivity and that if these subjects had been prospectively screened, then only three HSRs would have been prevented and the other six would still have occurred. This was extremely misleading in the light of all the available evidence and only referred to clinically-suspected HSRs rather than the more robust measure of immunologically-confirmed HSR.

When prospective screening was used, the diagnosis rate of HSR had been shown to reduce significantly if a clinician knew that a patient was HLA-B*5701 negative (Rauch *et al*). Indeed, in PREDICT-1 only 3.4% vs 7.8% of patients were diagnosed with a clinically-suspected HSR in the prospective screening arm vs the control arm. None of these subjects went on to have an immunologicially-confirmed HSR indicating that the majority of these diagnoses were misdiagnoses and not true HSR (Mallal *et al*, 2007).

Although factually correct, the statement could easily be misinterpreted as meaning that two-thirds of Kivexa HSR cases were in patients who did not possess the HLA-B*5701 allele. This ambiguity was due to the open-label design meaning that only patients in the Kivexa arm would have been suspected of being at risk of HSR and thus diagnosed as such in response to one or more symptoms raising clinical suspicion. In a blinded study suspected-HSRs could also have been diagnosed in the Truvada arm. Clinical diagnosis of HSR had occurred in non-abacavir arms in blinded studies eg CNA30024 where 3% abacavir HSR was reported in the zidovudine arm (DeJesus *et al*, 2004).

GlaxoSmithKline alleged that the statement at issue was ambiguous and misleading in breach of Clause 7.2. Additionally, GlaxoSmithKline alleged that the tone of the claim disparaged Kivexa in breach of Clause 8.1. The statement cast doubt over the robustness of current evidence for the utility of HLA-B*5701 screening from the PREDICT-1 study, which was a highly regarded and robust study also presented at the IAS conference.

In its response of 5 October, Gilead correctly noted that HLA-B*5701 screening was not standard care when the study was initiated, hence the use of retrospecting screening. However, Gilead refused to accept any disparagement on its part of the use of HLA screening.

Given the limitations of the BICOMBO study design, GlaxoSmithKline alleged that Gilead's interpretation of the data to support the promotion of Truvada was misleading in breach of Clauses 7.2, 7.3, 7.4, 8.1 and 9.1.

Since writing to Gilead, GlaxoSmithKline received a copy of a report issued by the IAS entitled 'New research and its implications for policy and practice', in which it praised the validation of genetic screening in the PREDICT-1 study and contrasted this against the study design issues regarding use of genetic screening encountered in the BICOMBO study:

> 'For clinical investigators, BICOMBO trial results underscore difficulties in planning and interpreting comparisons of two regimens in a rapidly evolving treatment environment. Had the trial incorporated HLA-B*5701 screening for abacavir hypersensitivity (instead of using it retrospectively), a small but perhaps critical number of participants may not have stopped abacavir for feared hypersensitivity and thus would not have been counted as 'failures'. Treatment advocates must ensure their constituencies are provided with fastidious and objective appraisals of such trial results in terms understandable to the layperson.'

RESPONSE

Gilead noted that current treatment of HIV patients naïve to therapy was based mainly on a backbone of two nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) as recommended by most national and international guidelines.

In randomised controlled trials this combination of 2NRTIs + 1NNRTI had provided the best efficacy and safety results. Currently in Europe, the most commonly prescribed NRTIs in naïve patients were the new fixed dosed combination tablets of either Truvada or Kivexa. The older combination Combivir (zidovudine and lamivudine) was now less frequently recommended in guidelines for naïve patients due to its toxicity profile compared to the newer combinations, so that patients stable on treatment were increasingly being switched to Kivexa or Truvada.

At present, comparative assessments of efficacy and toxicity between Kivexa and Truvada in naïve patients could only be drawn indirectly from results of randomised clinical trials of Kivexa or Truvada vs Combivir or other NRTIs with efavirenz. A large independent randomised clinical trial (ACTG5202) had recently been set up to compare Kivexa and Truvada head-to-head in naïve patients, however data from this long term trial was not expected for another 2 years.

The BICOMBO study was a robust independent, investigator-led study to compare the efficacy and safety of a switch to either Kivexa or Truvada in virologically controlled patients. This was an important study because it was the first randomised comparison of Kivexa and Truvada and provided the first head-to-head results allowing comparisons to be drawn between these two NRTI combinations in this setting. The study would run for 3 years and the first 48 week results were recently presented at a major HIV conference. Because of its uniqueness, the BICOMBO study results were likely to generate valuable scientific debate until ACTG5202 reported in 2009. As with all science, Gilead welcomed discussion and debate of this valuable new data.

Gilead agreed with GlaxoSmithKline that one of the fundamental principles of the Code when using a study to promote a product was that claims made must represent the balance of evidence available as well as being supportable by robust data. The leavepieces at issue were an accurate summary of the BICOMBO

study results and conclusions as presented at IAS 2007 and Gilead believed that sufficient information was presented to allow the reader to make a fair assessment of the study.

The BICOMBO study was first proposed to Gilead and GlaxoSmithKline in 2004 by an international group of HIV experts. The investigators were all based in Spain, where the study was exclusively conducted. The study proposal and protocol were submitted to each company by the investigators. The study proposal and all components of the protocol including study design, efficacy endpoints, safety analysis, randomisation procedures and the statistical methodology were assessed by Gilead before March 2005 when the company finally agreed to support the study. Gilead understood that both it and GlaxoSmithKline believed that the study had merit and import and had therefore agreed to co-fund it. The investigators shared the 48 week data with both companies prior to presenting it as a 'late-breaker' oral presentation at the IAS meeting in July, 2007.

With regard to inter-company dialogue, Gilead refuted GlaxoSmithKline's implication that Gilead had not responded in a timely and adequate manner to its concerns; Gilead had entered into dialogue in good spirit in a timely and constructive fashion. Gilead had responded to GlaxoSmithKline's concerns in a positive manner with a view to maintaining the highest scientific standards and complying with all applicable regulations, law and the Code.

Gilead did not agree with GlaxoSmithKline's allegations, however Gilead had agreed to amend the promotional materials at certain points by 30 October 2007, to improve clarity and enhance clinical discussion. All such proposed amendments were accurate and in line with the results and conclusions of the lead investigator's presentation. GlaxoSmithKline has rejected Gilead's offer for representation of the two companies to meet to further discuss the materials in an attempt to resolve the ongoing dispute.

Bias in randomisation

As stated by GlaxoSmithKline and clearly indicated at the top of both leavepieces, the BICOMBO study was an investigator-initiated and managed study, jointly funded by Gilead and GlaxoSmithKline. Throughout Gilead's dialogue with GlaxoSmithKline, Gilead had made it very clear that the contents of both leavepieces were accurate summaries of the results and conclusions presented at IAS 2007.

In BICOMBO, full randomisation of study subjects was performed by the investigator team in the manner approved by an independent statistician under the terms of the study protocol (randomisation was centralised and random numbers generated by means of a computer programme). The data was analysed by the Epidemiology and Statistics Unit, Hospital Clinic in Barcelona. In addition the results of the BICOMBO study had been peer-reviewed by the IAS faculty before the data was accepted as an oral presentation at its 2007 meeting.

GlaxoSmithKline had alleged that the BICOMBO study was flawed as 34% of patients assigned to the Truvada arm were already taking tenofovir at baseline and that only 7% of patients assigned to the Kivexa arm were already on abacavir at baseline. Market share data for the two combinations in Spain and the rest of Europe would have been readily available to any pharmaceutical company at the time of study review. The baseline imbalance in the two arms of the study could be anticipated because of the different market share of the two products in Spain. At IAS 2007, in response to a question from the floor, a subgroup analysis of the results with the prior drug exposure imbalance corrected, was presented and this demonstrated that there was no effect on the study conclusions.

Since the IAS presentation in July 2007, a further more complete analysis of the effects of this difference in prior product exposure had been formally analysed and presented at the EACS 2007 conference (Sanz *et al*) and this confirmed the results of the full study group that was previously presented at IAS 2007. This sub-analysis, excluding patients previously exposed to tenofovir or abacavir reached the same conclusions as the IAS presentation.

GlaxoSmithKline had agreed to continue funding of the BICOMBO study for 2008 and had been able to comment on the results before making this decision. Moreover, GlaxoSmithKline accepted the study design in providing its initial funding support in 2005.

However, it was important to note that there was no significant bias in the numbers of patients taking tenofovir at baseline who were then assigned to Truvada arm (34%) or Kivexa (26%) and also in the proportion of patients taking abacavir at baseline who were then assigned to Truvada (11%) or Kivexa (7%). The arms were well-balanced at baseline for these and other factors, with the exception that more Kivexa patients were still on their first antiretroviral regimen (29%) compared to the Truvada arm (17%), (p=0.01) over a similar median time of previous antiretroviral exposure (4.2 years, Kivexa; vs 3.7 years, Truvada). This greater treatment experience in terms of changes of antiretroviral regimen prior to study entry was likely to have benefited Kivexa rather than Truvada, as there would be greater risk of resistance and treatment failure in those that had changed treatments more frequently.

Gilead noted that as a condition of inclusion, patients had to be virologically suppressed and stable on treatment ie HIV RNA,< 200 copies per mL for six months or longer prior to randomisation. Such a stable viral treatment picture indicated that the likelihood of virological failure during the study was unlikely and was a general requirement of studies involving the switch of anti-retroviral drugs. The design of the study tested whether switch to either Kivexa or Truvada in stable and virologically suppressed patients maintained both virological control and a favourable safety profile.

Gilead therefore believed that the presentation of the

BICOMBO results was fair and balanced with sufficient information to allow readers to reach their own conclusions.

Baseline resistance testing

Baseline resistance testing was now generally regarded as necessary prior to starting treatment in naïve patients. However in the UK, this requirement had only recently been incorporated into guidelines for all naïve patients (BHIVA 2006) and adoption of these guidelines varied widely in Europe. Patients started on treatment prior to 2006 generally did not have baseline resistance tests performed and fully suppressed patients could not have resistance tests done at study entry, because their viral load was undetectable.

In the BICOMBO study, patients had been treated for a median of 4.2 years (Kivexa) and 3.7 years (Truvada). Baseline resistance testing was not undertaken at study entry as patients were already on treatment and this had not been a common practice in Spain when the BICOMBO study was planned or started and as such was not included within the protocol. Indeed baseline resistance testing was reserved for studies in treatment-naïve patients or for patients failing on treatment, neither of which applied here. There were several other examples of treatment-switch studies that had not required the availability of baseline resistance test as inclusion criteria, for example the RAVE study and the SWEET study, as the study population was treatment experienced. A requirement that there was no known previous virological failure and no documented resistance, was generally considered adequate in these studies.

Endpoints

BICOMBO was a non-inferiority study of Kivexa vs Truvada with an upper limit of 95% CI of estimated difference < 12.5%. This study design had been widely used to compare both naïve and experienced patients in various settings.

The primary endpoint of the BICOMBO study was the proportion of patients with treatment failure for any reason through week 48. This included virological rebound (> 200 copies/mL), discontinuation of study therapy or patients lost to follow-up, progression to a new late stage event or death.

The secondary endpoints were: the proportion of patients with virological failure at or before week 48 confirmed on-study HIV RNA ≥ 200 copies/mL or last on-study HIV RNA ≥ 200 copies/mL followed by discontinuation; time to treatment failure and to virological failure; CD4 changes; safety; and changes of fasting plasma lipids, body fat, bone mineral density and renal function.

With regard to the efficacy outcomes leavepiece, Gilead submitted that the primary endpoint of treatment failure was visually displayed as the first bar chart with the statistical data above in the graphics window and showed that Kivexa did not meet the non-inferiority endpoint compared to Truvada. The bullet points 'Treatment failure rates for Kivexa were 6% higher than Truvada' and 'For treatment efficacy, Kivexa did not meet the non-inferiority endpoint compared to Truvada',

These were statements of fact supporting the primary endpoint bar chart on the left of the panel. One of the secondary endpoints, the proportion of patients with virological failure, was addressed to the left of the primary endpoint in the panel with two supporting bullet points 0% virological failure for patients switched to Truvada' and 'For virologic efficacy, Kivexa met non-inferiority criteria compared to Truvada: however, there were more failures with Kivexa (2.4%) than Truvada (0%)'.

The second bullet point stated that non-inferiority was met but that there were more failures in the Kivexa arm. This again was a statement of fact relating specifically to this study.

Gilead denied that the efficacy outcomes leavepiece breached Clauses 7.2 and 7.3. The study was powered for non-inferiority for treatment failures, the primary efficacy endpoint. Kivexa did not meet this endpoint compared to Truvada. The efficacy leavepiece did not mention 'superiority' as the study was not powered for superiority and therefore Gilead denied a breach of Clauses 7.2 and 7.3.

The efficacy outcomes leavepiece addressed the primary endpoint (visually displayed as the first bar chart) and then went onto highlight important secondary efficacy endpoint areas. The claims made in the three bullet points accurately represented the conclusions of the the BICOMBO study as presented to IAS. GlaxoSmithKline then complained that '...there was a difference in the baseline regimens of the two groups, the randomisation has generated an inherent bias'. As stated previously, GlaxoSmithKline would have reviewed the protocol before deciding to fund the study and any areas of concern should have been raised then. The fact that GlaxoSmithKline failed to raise such concerns at this point must indicate that it was satisfied with the study design, or accepted such concerns as inconsequential on approving provision of continued funding to the study. In Gilead's opinion, these points were being raised now in order to explain study results and conclusions that were not favourable to GlaxoSmithKline. In addition Gilead believed that any potential bias in randomisation was part of the study design and would actually favour Kivexa. Gilead believed that the study was powered appropriately and any suggestion to remove data relating to patients receiving abacavir in the Kivexa arm and tenofovir in the Truvada arm was disingenuous.

The efficacy outcomes leavepiece was, as stated prominently at the top, intended to discuss 'Study Highlights'. It related solely to a study pre-examined and co-funded by the two companies. In faithfully representing the data as presented at the IAS conference, the leavepiece addressed the primary and main secondary efficacy endpoints. However for clarity, Gilead had agreed to add the table on baseline therapy from the IAS presentation to the leavepiece in

order that any baseline bias that could potentially favour Kivexa might be discussed with clinicians. In addition, Gilead had agreed to include the statistical bars from the presentation to replace the statistical figures which appeared above the bar charts in the first version of the leavepiece for visual simplicity.

Absence of baseline resistance testing

As stated above, baseline resistance testing was not performed in this study and it was not common practice to perform this in stable treatment-experienced patients. GlaxoSmithKline's concerns about baseline resistance testing could have been aired or would have been accepted by GlaxoSmithKline before it decided to fund the BICOMBO study. The presentation at the IAS included a slide showing that none of the four patients with virological failure in the Kivexa arm had been exposed to abacavir prior to the study, and that virological failure developed between months 4-8 of the study. The four patients had therefore been treated with an alternative lamivudine-based regimen (according to protocol) on which they had exhibited virological stability 'for 1-5 years', before entry to the study. That was, an HIV RNA viral load of < 200 copies /mL had been maintained for ≥ 6 months and that on change to Kivexa (also a lamivudine-based regimen), these patients failed virologically. This might point to a relative weakness of Kivexa compared to Truvada in the setting of treatment switch, however, the number of failures was few in number so that the non-inferiority criteria for this end point was met.

There were more patients in the Truvada arm who were more treatment experienced in that more patients had had more than one course of antiretroviral therapy. Previous treatment failure might theoretically predispose to viral resistance developing, as breaks and gaps in effective treatment might possibly have occurred in changes of antiretroviral regimen. Counter to GlaxoSmithKline's claim, it could therefore be argued that given the baseline data, patients in the Truvada arm were at greater risk of virological failure than those on Kivexa. However there were no failures on Truvada in this study.

As stated in inter-company communication, Gilead proposed to include the relevant baseline data table in the efficacy leavepiece in order to improve its clarity. Gilead also proposed to add a cartoon of the relevant statistics to ensure that those unfamiliar with non-inferiority trial designs and interquartile range statistics might better understand the non-inferiority test. Gilead denied breaches of Clauses 7.2 and 7.3.

*Retrospective HLA-B*5701 screening and open-label study design*

The efficacy outcomes leavepiece contained the wording 'Retrospective HLA-B5701 testing showed of 9 suspected HSR in the Kivexa arm, only 3 were HLA +ve'.

This was a statement of fact from the conduct of the study as presented by the principal investigator. HLA testing had not been part of standard clinical practice in the great majority of countries of the world and was not standard practice when the study protocol was designed. Indeed, other GlaxoSmithKline-sponsored studies (HEAT, ALOHA and SHARE which were currently running) initiated at the same time as BICOMBO did not include baseline HLA testing.
As an open label design, the BICOMBO study reflected 'real life' clinical practice and therefore under such circumstances a higher degree of suspicion of abacavir-related hypersensitivity was likely to exist, as this reaction could be confused with other symptoms and signs. Gilead noted that Section 4.4 of the Kivexa SPC stated:

> 'In clinical studies approximately 5% of subjects receiving abacavir develop a hypersensitivity reaction. Some of these cases were life-threatening and resulted in a fatal outcome despite taking precautions.' 'It is estimated that approximately 50% of patients with the HLA-B*5701 allele develop a suspected hypersensitivity reaction (HSR) during the course of abacavir treatment versus less than 3% of patients who do not have the HLA-B*5701 allele in the Caucasian population.' 'However, it is noteworthy that among patients with a suspected hypersensitivity reaction, 50% did not carry the HLA-B*5701 in the Caucasian population. Therefore, the clinical diagnosis of suspected hypersensitivity to abacavir must remain the basis for clinical decision-making.
> '

Of the 167 patients randomised to Kivexa, nine were suspected of developing abacavir hypersensitivity. This equated to 5% of the Kivexa study arm and accorded very well with data from other studies and the statement on HSR in the Kivexa SPC, mentioned above. Of these nine patients, six were shown retrospectively to be HLA-B*5701 negative, a proportion similar to that noted in the Kivexa SPC 'among patients with a suspected hypersensitivity reaction, 50% did not carry HLA-B*5701 in the Caucasian population'. As the BICOMBO study was conducted entirely in Spain, then the data were congruent with this prevalence statement about a Caucasian population.

In addition, the PREDICT study presented by GlaxoSmithKline at the 2007 IAS meeting concluded that 'GlaxoSmithKline continues to recommend the role of ongoing clinical vigilance in the management of HIV patients, regardless of the effectiveness of other tools available'. This was consistent with Gilead's statement in the efficacy leavepiece that 'clinical vigilance for HSR is essential during treatment'. It was incumbent upon the pharmaceutical industry to maintain awareness amongst health professionals of potentially serious issues associated with the use of medicines, as GlaxoSmithKline did with its Kivexa promotional materials regarding HSR. As Kivexa was mentioned in the efficacy leavepiece, Gilead had a duty to address HSR as part of overall safety concerns.

The detailed explanation by GlaxoSmithKline's detailed explanation of HLA-B*5701 and HSR testing in its letter of 21 September to Gilead represented a misinterpretation of the leavepieces. Gilead's statement

on the study numbers who underwent retrospective HLA-B5701 testing was not ambiguous or misleading in nature and was not in breach of either Clause 7.2 or 9.1. At no point had Gilead denigrated HLA testing. Gilead strongly denied that the efficacy leavepiece disparaged Kivexa or HLA-B*5701 testing and Gilead denied breaches of Clauses 7.2, 7.3, 8.1 and 9.1.

PANEL RULING

The Panel noted that the BICOMBO study was the first to directly compare the efficacy and safety of Kivexa and Truvada. The study would run for three years but to date data was only available from the first 48 weeks of the study and this had been presented in abstract form and orally at the IAS in July 2007. The study had thus not run its course and there was limited data in the public domain with regard to study design, statistical methods etc. The study was designed to assess the non-inferiority of the two combinations with respect to treatment efficacy (primary endpoint) and virological efficacy (secondary endpoint). Kivexa failed to meet the primary non-inferior endpoint compared with Truvada. The authors suggested that this might have been because some patients had to discontinue Kivexa treatment due to abacavir hypersensitivity reactions (discontinuation of study therapy was regarded as treatment failure). In terms of virological efficacy Kivexa met non-inferiority criteria compared with Truvada however there were more failures with Kivexa than Truvada (2.4% vs 0% respectively).

The Panel noted that the efficacy leavepiece featured a bar chart detailing treatment failure and virological failure. The visual impression of the bar chart was that Truvada was superior to Kivexa although this had not been shown statistically. Although the results favoured Truvada, the study was not powered to show superiority; in any event only 48 week data was available from a study which still had over 2 years to run. The following claims appeared to the right of the bar chart: 'For virologic efficacy, Kivexa met non-inferiority criteria compared to Truvada; however there were more failures with Kivexa (2.4%) than Truvada (0%)'; 'Treatment failure rates with Kivexa were 6% higher than Truvada' and 'For treatment efficacy, Kivexa did not meet the non-inferiority endpoint compared to Truvada.'

The Panel noted that although Kivexa had not been shown to the non-inferior to Truvada in terms of treatment efficacy, Truvada had not been shown to be superior. In terms of virological efficacy Kivexa was shown to be non-inferior to Truvada although there were more treatment failures with Kivexa than Truvada. The Panel considered that although the interim data from the BICOMBO study was of undoubted interest, but noted that the study had yet to run its full course. In that regard the Panel noted the supplementary information to Clause 7.2 of the Code which stated that where a clinical or scientific issue exists which has not been resolved in favour of one generally accepted viewpoint, particular care must be taken to ensure that the issue is treated in a balanced manner in promotional material.

The Panel considered that the efficacy outcomes leavepiece implied that Truvada had been shown to be superior compared with Kivexa which was not so. The Panel considered that the claims detailed above were misleading as alleged. Breaches of Clauses 7.2 and 7.3 were ruled.

The Panel noted that the leavepiece at issue did not record the fact that no baseline resistance testing had taken place although it did state that at baseline patients had been virologically suppressed for at least 6 months. The definition of suppression (<200 copies HIV RNA per ml) was not stated although virological failure was stated to be ≥200 copies/ml. The Panel noted Gilead's submission that baseline resistance testing could not have been performed at study entry due to the viral load being undetectable.

Overall the Panel considered that whilst it might have been helpful for readers of the leavepiece to know that baseline testing had not been carried out, the omission of such data was not misleading per se. Readers were told that patients were virologically suppressed at baseline. On balance the Panel considered that the claims 'For virological efficacy, Kivexa met non-inferiority criteria compared to Truvada; however there were more failures with Kinvexa (24%) than Truvada (0%)' and 'For treatment efficacy, Kivexa did not meet the non-inferiority endpoint compared to Truvada' were not misleading on this point and ruled no breach of Clause 7.2.

The Panel considered that the claim 'Retrospective HLA-B5701 testing showed of 9 suspected HSR in the Kivexa arm, only 3 were HLA positive. Clinical vigilance for HSR is essential during treatment' clearly referred to suspected HSR and not immunologically-confirmed HSR. The Panel noted that the claim implied that 6 cases of suspected HSR were in patients who were HLA negative. Section 4.4 of the Kivexa SPC referred to the possibility of suspected HSR in patients who did not carry HLA-B*5701. The Panel did not consider the claim at issue was misleading, ambiguous or incapable of substantiation nor did it disparage Kivexa. No breach of Clauses 7.2, 7.3, 7.4 and 8.1 was ruled.

Although noting its comments above the Panel did not consider that high standards had not been maintained. No breach of Clause 9.1 was ruled.

2 Leavepiece entitled 'Study highlights: BICOMBO – safety outcomes'.

COMPLAINT

GlaxoSmithKline was concerned that Gilead had not properly considered its complaints regarding the following claim made in the safety outcomes leavepiece:

> 'Switching virologically suppressed patients to Truvada provides a significantly more favourable lipid profile* than Kivexa, with no differences in renal function or bone mineral density'. (The

asterisk referred to TG, TC and LDL and was shown as a footnote.)

In its letter of 24 August, GlaxoSmithKline alleged that it was misleading to claim that Truvada had a significantly better lipid profile than Kivexa based on only three of the four parameters measured, as the fourth (HDL) was widely believed to be an important factor when evaluating cardiovascular risk, as in the Framingham calculator and the British Heart Foundation guidelines. TGs were understood to play a minor role.

Use of the asterisk and footnote were inappropriate. Clearly Gilead's representation of these data was selective and misleading and should report all four lipid results in a balanced manner, rather than excluding the clinically relevant parameter of HDL which improved significantly in the Kivexa arm of the study.

In its response Gilead argued that the lipid profiles demonstrated in the BICOMBO study were entirely consistent with the findings of a number of other studies, but only one of these (RAVE) directly compared tenofovir and abacavir. The RAVE study demonstrated small but statistically significant differences in favour of tenofovir for TC, LDL and TG (Moyle GJ *et al*). HDL did not change from baseline in the abacavir arm of the RAVE study but fell slightly in the tenofovir arm; the difference between the two treatment arms as regards HDL did not reach statistical significance. Importantly, the clinical relevance of the lipid changes reported in the RAVE study with regard to cardiovascular risk remained uncertain. The RAVE study had its limitations too, as there were only around 50 patients in each arm of the study and the tenofovir and abacavir arms in this study were not balanced as regards use of stavadine and zidovadine at baseline – proportionately more patients in the Truvada arm were on stavadine at baseline compared with the Kivexa arm (77% v 59%) and this constituted a major criticism of the study.

BICOMBO was the first comparative study between Truvada and Kivexa to provide TC/HDL ratios as the RAVE study did not do so.

In BICOMBO, HDL worsened on Truvada and the TC:HDL ratio remained unchanged for both Truvada and Kivexa. Following the dialogue, Gilead had agreed to amend 'the text of the first bullet point of the Gilead safety leavepiece to report on all four lipid results'. Gilead subsequently confirmed that it would remove the asterisk and qualified claim that would otherwise be in breach of the supplementary information to Clause 7. GlaxoSmithKline thus expected that Gilead would qualify the broad lipid claim made to provide the appropriate balance as given by the HDL data.

Despite these concessions, Gilead had not agreed to modify the claim 'switching to Truvada provides a significantly more favourable lipid profile than Kivexa'. This was clearly misleading and all embracing even with Gilead's proposed concessions. Thus GlaxoSmithKline believed that on this point inter-company dialogue had failed (as per Gilead's letters of 5 and 10 October) and that this claim was in breach of Clause 7.2.

Furthermore GlaxoSmithKline was concerned that the claim 'Switching to Truvada provides a significantly more favourable lipid profile than Kivexa' was misleading with regard to the safety of Truvada. The Truvada summary of product characteristics (SPC) listed hypertriglyceridaemia as a commonly reported adverse event, and cautions regarding hypercholesterolaemia in combination antiretroviral therapy in section 4.8 (with reference to section 4.4). This was likely to be in breach of Clause 7.10 by not encouraging the rational use of the medicine.

GlaxoSmithKline did not find Gilead's response to the fact that hypertriglyceridaemia was present as an adverse event in the Truvada SPC satisfactory as the leavepiece clearly implied an improvement in triglycerides at variance with this important safety statement in the SPC. Gilead claimed that it was acceptable to cite such study conclusions when made by the investigator. Any results in relation to this study should be offset by reference to this important statement. GlaxoSmithKline alleged a breach of Clause 7.10. As above, statements made by investigators were not automatically suitable for inclusion in promotional material.

Finally, GlaxoSmithKline alleged that the Study highlights – safety outcomes leavepiece was misleading in that it did not mention the primary outcomes of the study. This was not a safety study. Secondary parameter claims could not be made without presenting the primary parameter data from the study to allow clinicians to assess the relative efficacy and safety of the two components. Gilead's assertion that the primary efficacy parameters were presented elsewhere (ie in a separate leavepiece) did not allay GlaxoSmithKline's concerns, as it considered that each piece must be capable of standing alone. GlaxoSmithKline reasserted its belief that this element was in breach of Clauses 7.2 and 7.10.

RESPONSE

Gilead explained that dyslipidaemia was common in HIV-infected and HIV-treated patients but the implications of dyslipidaemia in these patients were not fully known. At present there were no UK guidelines for the management of dyslipidaemia in HIV patients. To Gilead's knowledge, the only guidelines relating to the evaluation and management of dyslipidaemia in HIV patients emanated from the US.

The guidelines used as their basis the US National Cholesterol Education Program (NCEP) Expert panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel [ATP III]) criteria and algorithm. The NCEP ATP III identified five risk factors that modified the target levels to which LDL cholesterol should be brought, ie smoking, age, a family history of premature coronary heart disease, hypertension and a low HDL (< 1mmol/L) level

(diabetes was considered equivalent to the presence of coronary heart disease). If no or only one risk factor was present, then the goal to which LDL should be reduced to, if elevated, was 4.10mmol/L. If two or more risk factors were present then the goal was reduced to 3.33mmol/L. As low HDL cholesterol was one of the five risk factors, then it might not be important in the management of an elevated LDL cholesterol if, for example, two of the other risk factors were present, such as hypertension and a family history. The level of LDL cholesterol was considered the primary parameter on which to base management decisions by these guidelines, the HDL cholesterol level was secondary. As these guidelines represented the present state of management of dyslipidaemia in HIV patients then Gilead believed that the bullet point on the safety leavepiece 'Truvada showed a significantly more favourable lipid profile compared to Kivexa' was factually justified and did not breach Clauses 7.2 and 7.10.

The DAD (Data collection on Adverse events of anti-HIV Drugs) study was the largest prospective cohort of HIV patients worldwide, assessing morbidity and mortality due to cardiovascular disease, as well as liver failure and related death. As the factors contributing to cardiovascular risk in the HIV population were not well understood, the CHMP had recently recommended that the DAD cohort be continued to help in elucidating the role of antiretroviral therapy in cardiovascular risk.

Gilead had always accepted the value of the Framingham calculation for the non-HIV infected population. Gilead had never argued that HDL was not an important factor in cardiovascular risk; it had merely asserted that according to the published study results triglycerides, total cholesterol and low density lipoprotein indices improved on Truvada administration. In the interests of clarity, Gilead had already informed GlaxoSmithKline that the text of the first bullet point of the safety outcomes leavepiece would be amended to report on all four lipid results (TG, TC, LDL and HDL) in the bulleted text, to accompany the visual representation of the results, already prominently displayed in the piece, adjacent to the bullet. Gilead suggested that the following be added to its leavepiece to enable clinician discussion: 'The median fasting HDL level fell by 4 mg/dL (0.1 mmol/l) in the Truvada arm, and remained the same in the Kivexa arm, $p<0.0001$)'.

The BICOMBO study showed no change with respect to HDL on Kivexa treatment – this was not an improvement. On the contrary, treatment with Kivexa resulted in deteriorations in both TC and LDL whilst HDL and TG remained unchanged. For those on Truvada, according to the data, each of TG, TC and LDL improved but HDL declined in comparison with Kivexa.

The claim that 'Switching to Truvada provides a significantly more favourable lipid profile than Kivexa' was a comparative statement made by the investigators from their analysis of the results and not from a review of the SPCs of each of Truvada and Kivexa. The statement fell within the investigators' remit of being able to fairly report the results of their study and their analysis of them.

Whilst GlaxoSmithKline had correctly observed that the Truvada SPC listed hypertriglyceridaemia as a commonly reported adverse event, and had cautions regarding hypercholesterolaemia in combination antiretroviral therapy in section 4.8 of the SPC (with reference to section 4.4. of the SPC) this did not prevent independent study reporting and analysis. Furthermore, the statement in the Truvada SPC related to naïve patients that were started on tenofovir, not experienced patients who were switched from an existing NRTI backbone.

The comparative statement made by the investigators and repeated by Gilead arose from the comparison of the lipid profiles of Truvada and Kivexa from the results of the BICOMBO study. The BICOMBO study was a switch study in which patients had previously been on a variety of previous NRTI backbones which might have had unfavourable lipid profiles. Previous studies that had involved switching from one NRTI backbone to Truvada or to its component tenofovir, had consistently shown benefits in lipid profiles, including triglycerides.

There was no breach of Clause 7.10 as Gilead had presented the lipid data objectively, in context and without exaggerating Truvada's properties. In making such a statement, Gilead was fairly reporting the peer-reviewed clinical study results of an independent investigator.

The safety outcomes leavepiece did not mention the primary outcomes of the BICOMBO study. The safety data were secondary endpoints and the leavepiece was used in conjunction with the efficacy outcomes leavepiece by the representatives. The Code did not prevent the production of leavepieces which only discussed a secondary endpoint although conventionally both primary and secondary outcomes to a study could be presented at the same time. The supplementary information to Clause 4.1 stated that the material should be able to stand alone for example, and this could be achieved by having the prescribing information included within the piece. Whilst Gilead accepted that this was not a safety study per se, Gilead had presented the primary endpoint data from the BICOMBO study elsewhere, to allow clinicians to assess the relative efficacy and safety of the two components and Gilead representatives would continue to present both leavepieces to describe both the primary and secondary outcomes. When displayed, the leavepieces had also been displayed together to represent all the main findings of the study. Gilead proposed that it also added the words 'Primary endpoint' and 'Secondary endpoints' to the leavepieces as appropriate, to make this information clearer.

In summary, the BICOMBO study was an important study because it was the first head-to-head randomised trial to compare the performance of Kivexa and Truvada in the setting of virologically controlled HIV positive patients, who required switching their

medicines. Gilead believed that the BICOMBO study was a robust independent investigator-led study worthy of summary and discussion and it welcomed discussion and debate of this valuable new data.

Gilead firmly believed that the leavepieces accurately summarised the BICOMBO results and conclusions as presented at IAS 2007 and that sufficient information was presented to allow the reader to make a fair assessment of the study results and conclusions.

PANEL RULING

The Panel noted that although Gilead had agreed to refer to all four lipid results (TG, TC, LDL and HDL) in its claims regarding lipid profile, it had not agreed to modify the claim 'Switching virologically suppressed patients to Truvada provides a significantly more favourable lipid profile …'. The results shown to substantiate this claim were the absolute changes in lipid levels over 48 weeks and the lack of change in the TC/HDL ratio over the same time period. However, although, for instance, readers were told that LDL rose by 7mg/dL over 48 weeks there was no indication as to the clinical significance of this. The Panel considered that the information given was such that prescribers would be unable to form their own opinion as to the clinical significance of the results; the leavepiece was thus misleading in this regard. A breach of Clause 7.2 was ruled.

The Panel noted that the leavepiece depicted a decrease in triglycerides (-16mg/dL) over 48 weeks. The Truvada SPC, however, listed hypertriglyceridaemia as a common side-effect. The Panel considered that it was misleading to refer to the observed decrease in triglycerides without noting the statement in the SPC regarding hypertriglyceridaemia. A breach of Clause 7.10 was ruled as alleged.

The Panel did not consider that it was necessarily unacceptable to produce a leavepiece focussing only on the safety data when such data had come from secondary endpoints of a study. None of the primary end-points were safety-related and so in that regard the safety data was capable of standing alone. However the leavepiece at issue did not make it clear that the data presented was from secondary endpoints and that primary endpoints had related to efficacy. Some readers might assume that the BICOMBO study was primarily a safety study which was not so. The leavepiece was misleading in this regard. Breaches of Clauses 7.2 and 7.10 were ruled.

Complaint received	**12 October 2007**
Case completed	**7 January 2008**

CASE AUTH/2059/10/07

PRIMARY CARE TRUST MEDICINES MANAGEMENT DIRECTOR v JANSSEN-CILAG

Risperdal Consta journal advertisement

A primary care trust medicines management director alleged that an advertisement for Risperdal Consta (risperidone, long-acting injection) issued by Janssen-Cilag was misleading. The advertisement featured a lone female figure in a playground walking away from a trail of articles which included a doll, photograph album, wedding veil, handbag, toothbrush and hairbrush.

The complainant alleged that the advertisement depicted a child who was clearly under 18 years of age. The complainant's immediate opinion on seeing the advertisement was that Risperdal Consta could be prescribed for a young teenager. A doll lying on the ground reinforced this impression. Conversely the prescribing information stated that the product had not been studied in children and adolescents under 18.

The Panel considered that the photograph depicted a lone figure apparently walking away from her own possessions. The figure was casually dressed and had her back to the camera; it was impossible to know how old she was. The impression that the figure had possibly once owned the articles on the ground was compounded by the adjacent text 'Prescribe early, because what she loses, she could lose forever'. The Panel queried how many readers would interpret the articles, as submitted by Janssen-Cilag, as representing things that the girl might never have ie marriage, motherhood etc. Further, the statement 'Prescribe early' implied that the figure in the photograph was a young person. The Panel noted that the Risperdal Consta summary of product characteristics (SPC) stated that the product had not been studied in children or adolescents younger than 18 years. The Panel considered that it had not been made sufficiently clear that the girl in the advertisement was at least 18 years of age. In that regard the Panel considered that the advertisement was misleading as alleged and inconsistent with the SPC. Breaches of the Code were ruled.

A primary care trust medicines management director complained about an advertisement (ref RISP/C/06-0038) for Risperdal Consta (risperidone, long-acting injection) issued by Janssen-Cilag Ltd. The advertisement featured a lone female figure in a playground walking away from a trail of articles which included a doll, photograph album, wedding veil, handbag, toothbrush and hairbrush.

COMPLAINT

The complainant alleged that the advertisement depicted a child who was clearly under 18 years of age. The complainant's immediate opinion on seeing the advertisement was that Risperdal Consta could be prescribed for a young teenager. A doll lying on the ground reinforced the complainant's impression of a child. Conversely the prescribing information stated that the product had not been studied in children and adolescents under 18. The complainant alleged that the advertisement was misleading and should be withdrawn.

The Authority asked Janssen-Cilag to respond in relation to the requirements of Clauses 3.2, 7.2 and 7.8 of the Code.

RESPONSE

Janssen-Cilag submitted that the advertisement used apparently 'dropped' articles as visual metaphors for the devastating effects of schizophrenia. It was meant to outline the potentially detrimental outcomes for individuals who suffered recurrent relapses of schizophrenia. These included the possible loss of beneficial behaviours, such as self hygiene and financial management and being denied the opportunity of experiencing life events enjoyed by non-affected individuals, such as marriage, childbearing and other interpersonal relationships

There was not, and never was, any intention to imply that Risperdal Consta should be used in children. The image did not represent an individual less than 18 years of age. The model featured in the advertisement was in fact 33 years of age. In addition, Janssen-Cilag considered that the style of both the handbag and its contents, the visual symbols of marriage (the veil), relationships (the photo album) were not consistent with articles commonly carried by, or associated with, 'young teenagers' or indeed with teenagers younger than 18.

Janssen-Cilag disagreed with the complainant's statement that the doll lying on the ground reinforced the impression of a child, as the average teenage girl would not carry a toy doll. The doll referred to potential motherhood, not the subject's own childhood, as should be clear from the context of the other dropped objects.

Janssen-Cilag stated that it had not received any other such comments or complaints about the advertisement. The company was convinced that the majority of health professionals seeing the advertisement would not gain the impression it was promoted the use of Risperdal Consta in children under the age of 18 years.

The company therefore denied breaches of Clauses 3.2, 7.2 and 7.8 of the Code.

PANEL RULING

The Panel considered that the photograph depicted a lone figure apparently walking away from her own possessions. The figure was casually dressed and had her back to the camera; it was impossible to know how old she was. The impression that the figure had possibly once owned the articles on the ground was compounded by the adjacent text 'Prescribe early, because what she loses, she could lose forever'. In that regard the Panel queried how many readers would interpret the articles as representing things that the girl might never have ie marriage, motherhood etc. Further, the statement 'Prescribe early' implied that the figure in the photograph was a young person. The Panel noted that the Risperdal Consta summary of product characteristics (SPC) stated that the product had not been studied in children or adolescents younger than 18 years. The Panel considered that it had not been made sufficiently clear that the girl in the advertisement was at least 18 years of age. In that regard the Panel considered that the advertisement was misleading as alleged and inconsistent with the particulars listed in the Risperdal Consta SPC. Breaches of Clauses 3.2, 7.2 and 7.8 were ruled.

Complaint received	**17 October 2007**
Case completed	**14 November 2007**

CASES AUTH/2061/10/07 and AUTH/2062/10/07

WYETH v LILLY and BOEHRINGER INGELHEIM

Cymbalta detail aid

Wyeth complained about the claim 'Cymbalta vs venlafaxine XL – Cymbalta 60mg OD had similar efficacy to venlafaxine XL 150mg OD' in a primary care detail aid for Cymbalta (duloxetine) issued by Lilly and Boehringer Ingleheim. Cymbalta was indicated, *inter alia*, for the treatment of major depressive episodes. Wyeth supplied Efexor XL (venlafaxine).

Wyeth noted that the claim at issue was referenced to Perahia *et al* (2007). As could be seen from the graph on the relevant page, Lilly was making a claim that the efficacy [of venlafaxine XL] was similar to that of Cymbalta. Wyeth asserted that such a claim needed to be backed by robust scientific evidence, such as a positive non-inferiority analysis.

Perahia *et al* included a non-inferiority efficacy analysis but it was negative. As the authors stated 'Duloxetine 60mg/day failed to meet the a priori-defined non-inferiority criteria for the comparison with venlafaxine 150mg/day at study period II and study periods II and III'. Thus as no robust statistical evidence to demonstrate that venlafaxine and Cymbalta had similar efficacy had been presented, Wyeth asserted that the claim should not have been made. Wyeth did not consider that Lilly's suggestion to change the wording above the graph to 'The efficacy of Cymbalta 60mg OD has not been shown to be different from venlafaxine 150mg XL OD', changed anything, as the impression was still that the medicines were equivalent even if it was only by implication.

Wyeth alleged that the current (and proposed) claim was misleading and exaggerated; to the extent that it had not been substantiated, there was a further breach. Wyeth also suggested that the graph did not conform to the spirit of the Code, which was also a breach.

The Panel noted that Wyeth had complained to Lilly and Boehringer Ingelheim about a detail aid. Following inter-company discussions the detail aid and others sales material had been withdrawn. The Director considered that it appeared that the inter-company discussion on the original detail aid had been successful in that the original claim had been withdrawn and thus the Panel was not required to rule on this detail aid. The new Cymbalta detail aid at issue 'Simplifying the approach to a difficult patient journey' described briefly on page 6 the design, objectives and results of Perahia *et al*. The section concluded with 'The primary objective was not met, however, on the outcome analysis, no statistical difference was seen between venlafaxine XL and duloxetine'. The page featured a graph showing the decrease (improvement) in HAM-D17 scores of Cymbalta 60mg once a day and venlafaxine XL 150mg once a day. The two lines of the graph were almost superimposed on one another. A heading to the graph stated 'In this study, the efficacy of Cymbalta 60mg OD has not been shown to be different from venlafaxine 150mg XL OD (response and return to normal functioning as measured by HAM-D17) – secondary endpoint'. The claim was referenced to Perahia *et al*. The bullet point 'With no direct evidence of difference in efficacy to venlafaxine XL 150mg OD' appeared beneath the graph.

The Panel noted that Perahia *et al* was the only published, peer reviewed, direct comparison of Cymbalta and venlafaxine. The authors had noted a number of limitations to their study. The authors stated that the results of the Global Benefit Risk assessment (the primary endpoint) suggested that Cymbalta and venlafaxine had a similar benefit-risk profile. Similarly the secondary efficacy measures also demonstrated little difference between the two. The authors concluded that additional head-to-head studies, including trials of longer duration, were warranted to determine if patients might have a better benefit-risk profile with one medicine compared with the other.

Overall the Panel considered that Perahia *et al* was a useful first comparison of Cymbalta and venlafaxine but that it had not proven the equivalence of Cymbalta and venlafaxine. More studies were needed. In that regard the Panel noted supplementary information to the Code which stated that where a clinical or scientific issue existed which had not been resolved in favour of one generally accepted viewpoint, particular care must be taken to ensure that the issue was treated in a balanced manner.

The Panel considered that the detail aid at issue implied that Cymbalta and venlafaxine had been shown, beyond doubt, to have equivalent efficacy which was not so. The detail aid was misleading in that regard. Breaches of the Code ruled. The unequivocal claim could not be substantiated. A further breach was ruled.

Wyeth Pharmaceuticals complained about a primary care detail aid (ref CYM 1008) for Cymbalta (duloxetine) issued by Eli Lilly and Company Limited and Boehringer Ingleheim Limited. Cymbalta was indicated, *inter alia*, for the treatment of major depressive episodes. Wyeth supplied Efexor XL (venlafaxine).

COMPLAINT

Wyeth complained about the claim 'Cymbalta vs venlafaxine XL – Cymbalta 60mg OD had similar efficacy to venlafaxine XL 150mg OD'. The claim was referenced to Perahia *et al* (2007). As could be seen from the graph on the relevant page, Lilly was making a claim that the efficacy was similar to that of Cymbalta. Wyeth asserted that such a claim needed to be backed by robust scientific evidence, such as a positive non-inferiority analysis.

Perahia *et al* included a non-inferiority efficacy analysis but it was negative. As the authors stated, 'Duloxetine 60mg/day failed to meet the a priori-defined non-inferiority criteria for the comparison with venlafaxine 150mg/day at study period II and study periods II and III'.

As Lilly had presented no robust statistical evidence to demonstrate that venlafaxine and Cymbalta had similar efficacy, Wyeth asserted that it should not be making such a claim. Wyeth did not consider that Lilly's suggestion to change the wording above the graph to 'The efficacy of Cymbalta 60mg OD has not been shown to be different from venlafaxine 150mg XL OD', changed anything, as the impression that doctors would receive, especially in the context of a promotional item, was that the medicines were equivalent even if it was only by implication.

Thus Wyeth alleged that the current (and proposed) promotion was misleading and exaggerated, in breach of Clauses 7.2 and 7.3. To the extent that the claim referred to above had not been substantiated, there was a breach of Clause 7.4. Wyeth also suggested that the graph did not conform to the spirit of the Code, which was a breach of Clause 7.8.

RESPONSE

Lilly and Boehringer Ingleheim (the Alliance) submitted similar responses.

The companies submitted that the claim 'Cymbalta 60mg OD had similar efficacy to venlafaxine XL 150mg OD' could be supported, Perahia *et al*. However, in the spirit of inter-company dialogue and in an effort to reach an acceptable resolution, the companies offered an amendment to clarify further that there was no difference between the treatment groups. This commitment was communicated to Wyeth on 7 September. The companies also committed to highlight that this claim was a secondary endpoint of the study.

The Alliance therefore offered to stop using this particular claim in sales material and all materials produced for use from 4 October had been amended with the new claim '… the efficacy of Cymbalta 60mg OD has not been shown to be different from venlafaxine 150mg XL OD (response and return to normal functioning as measured by HAM-D17) – secondary endpoint'.

Wyeth was not satisfied with this response and at a meeting in September attended by representatives from all three companies, it was clear that Wyeth did not believe that the Alliance should use this study in any promotional materials and that the new proposed wording was not acceptable.

Perahia *et al* described two pooled studies of similar study design. The pre-defined primary objective of these studies was to test the hypothesis that duloxetine 60mg/daily was statistically superior to venlafaxine XL 150mg/daily after 6 weeks of treatment using the GBR (Global Benefit Risk) measure. Whilst the primary endpoint did not demonstrate superiority of duloxetine 60mg/daily to venlafaxine 150mg/daily there was however no statistically significant difference between the GBR scores for the two treatment groups.

Secondary endpoints of the pooled studies included efficacy measures looking at response and remission rates as measured by the HAM-D17. The studies showed that although duloxetine failed to meet a further secondary endpoint of non-inferiority based upon change in HAM-D17 from baseline the response and remission rates were not significantly different between duloxetine 60mg/daily and venlafaxine XL 150mg/daily at 6 weeks (response rate of 51.6% and 54.5%; and remission rates of 31.4% and 35.2% respectively) and at 12 weeks (response rates of 62.6% and 69.1%; and remission rates of 48.1% and 50.3% respectively). It should be noted that response and remission rates were determined as a priori secondary objectives of this study.

Perahia *et al* was the only fully published peer-reviewed direct comparison of duloxetine and venlafaxine. Therefore this study represented the full balance of evidence to support the aforementioned claims relating to comparative efficacy of these two anti-depressants.

Wyeth submitted only one page of the detail aid, which only showed the graph and the efficacy claims without the study descriptor that was an important component of this detail aid. To be able to fully assess whether this material met the requirements of the Code, the Alliance believed that the detail aid needed to be considered in the context that it was presented to a health professional. The detail aid was specifically designed so that the adjacent page provided relevant information about the design and outcomes of the study.

The objective of the study descriptor 'Cymbalta vs Venlafaxine XL' page in the detail aid was to highlight the actual study design and describe the primary objective of the pooled studies as published; state upfront that the primary objective of the study was not met. (The GBR assessment did not demonstrate Cymbalta 60mg OD to be superior to venlafaxine XL 150mg) and detail the tolerability profile demonstrated for the anti-depressants.

Therefore this descriptor provided relevant information and context to the health professional when viewing the following adjacent page that outlined the secondary endpoint and related efficacy graph. Thus the Alliance did not agree that the graph used to

illustrate the secondary outcome of the study was misleading when coupled with the study descriptor.

In any event, the graph was a true and accurate representation of the graph shown in Perahia *et al* and therefore gave a fair and balanced view of the comparison between these two anti-depressants. The claim and graph were also clearly referenced. For this reason alone, the Alliance did not agree that the graph was misleading as alleged. In addition the claim, 'Cymbalta 60mg OD had similar efficacy to venlafaxine XL 150mg OD (response and return to normal functioning as measured by HAMD-17)' was fully substantiated by Perahia *et al*.

As this was the only published peer-reviewed paper that described a direct head-to-head comparison between Duloxetine and venlafaxine, and hence represented the full balance of evidence when directly comparing the efficacy and tolerability of these two treatments, the Alliance disagreed with Wyeth's assertion that there was a lack of robust scientific evidence to support this claim. Nonetheless, in an effort to resolve this issue at an inter-company level the Alliance committed to modify its promotional claims to: 'In this study, the efficacy of Cymbalta 60mg OD has not been shown to be different from venlafaxine 150mg XL OD (response and return to normal functioning as measured by HAM-D17) – secondary endpoint'.

The companies confirmed that the detail aid had now been updated accordingly. In the interest of inter-company dialogue a copy of this updated page was sent to Wyeth on 19 September. Hence the companies were very disappointed to note Wyeth's complaint about the former material.

The detail aid accurately stated that Cymbalta 60mg OD had not been shown to be different from venlafaxine XL 150mg OD (response and return to normal functioning as measured by HAM-D17) as a secondary endpoint since there was no statistically significant difference between response and remission rates. Also in the current detail aid the primary objective was clearly stated and the outcome detailed clearly upfront before the secondary outcome was illustrated.

Venlafaxine and duloxetine were the only two serotonin and noradrenalin reuptake inhibitors (SNRIs) currently available in the UK. The Alliance's sales team were frequently asked for any comparative data on the class of anti-depressant treatment by health professionals wishing to make informed treatment choices. Perahia *et al*, as previously stated, was the only published peer reviewed paper that described a direct head-to-head comparison between duloxetine and venlafaxine and hence represented the full balance of evidence when directly comparing the efficacy and tolerability of the two treatments.

The Alliance disagreed with Wyeth's assertion that such a claim needed to be backed by robust scientific evidence such as a positive non-inferiority analysis. The claim was an accurate reproduction of the results from Perahia *et al* that was considered worthy of publication in a psychiatric peer-reviewed journal and the pertaining evidence had not been challenged or contradicted by any subsequent evidence based studies.

The companies believed the aforementioned claims presented in both primary care details aids, CYM 1008 and 1072, accurately and fairly reflected the results of Perahia *et al*. Hence the companies did not believe that the claims were misleading or exaggerated and in breach of Clauses 7.2 and 7.3.

In addition the Alliance did not agree that the graph used to illustrate the secondary outcome of the study was misleading as alleged, as it was a true and accurate representation of the graph in Perahia *et al*. The Alliance did not agree, therefore, that this graph was in breach of Clause 7.8.

In this respect the Alliance believed that its primary care detail aid in its entirety had accurately represented the data to enable health professionals to interpret, evaluate and draw their own conclusions about the study and how it related to their own clinical practice.

PANEL RULING

The Panel noted that Wyeth had complained to Lilly and Boehringer Ingelheim about a detail aid (CYM 1008). Following inter-company discussions the detail aid and others sales material had been withdrawn. The Director considered that it appeared that the inter-company discussion on the original detail aid (CYM 1008) had been successful in that the original claim had been withdrawn and thus the Panel was not required to rule on this detail aid.

The Panel noted that the new Cymbalta detail aid at issue (CYM 1072) 'Simplifying the approach to a difficult patient journey' described briefly on page 6 the design, objectives and results of Perahia *et al*. The section concluded with 'The primary objective was not met, however, on the outcome analysis, no statistical difference was seen between venlafaxine XL and duloxetine'. The page featured a graph showing the decrease (improvement) in HAM-D17 scores of Cymbalta 60mg once a day and venlafaxine XL 150mg once a day. The two lines of the graph were almost superimposed on one another. A heading to the graph stated 'In this study, the efficacy of Cymbalta 60mg OD has not been shown to be different from venlafaxine 150mg XL OD (response and return to normal functioning as measured by HAM-D17) – secondary endpoint'. The claim was referenced to Perahia *et al*. The bullet point 'With no direct evidence of difference in efficacy to venlafaxine XL 150mg OD' appeared beneath the graph.

The Panel noted that Perahia *et al* was the only published, peer reviewed, direct comparison of Cymbalta and venlafaxine. The authors had noted a number of limitations to their study. The authors stated that the results of the GBR assessment (the primary endpoint) suggested that Cymbalta and venlafaxine had a similar benefit-risk profile. Similarly the

secondary efficacy measures also demonstrated little difference between the two. The authors concluded that additional head-to-head studies, including trials of longer duration, were warranted to determine if patients might have a better benefit-risk profile with one medicine compared with the other.

Overall the Panel considered that Perahia *et al* was a useful first comparison of Cymbalta and venlafaxine but that it had not proven the equivalence of Cymbalta and venlafaxine. More studies were needed. In that regard the Panel noted the supplementary information to Clause 7.2 of the Code which stated that where a clinical or scientific issue exists which has not been resolved in favour of one generally accepted viewpoint, particular care must be taken to ensure that the issue is treated in a balanced manner in promotional material.

The Panel considered that the detail aid at issue implied that Cymbalta and venlafaxine had been shown, beyond doubt, to have equivalent efficacy which was not so. The detail aid was misleading in that regard. Breaches of Clauses 7.2, 7.3 and 7.8 were ruled. The unequivocal claim could not be substantiated. A breach of Clause 7.4 was ruled.

Complaint received	**24 October 2007**
Case completed	**3 December 2007**

CASE AUTH/2063/10/07

CONSULTANT PHYSICIAN v ABBOTT

Invitation to an advisory board

A consultant physician alleged that an invitation from Abbott, to attend a renal care advisory board looked suspiciously like commercial promotion, or at least a kind of marketing focus group for directing sales tactics, not genuine consultation on clinical management as claimed. The company had offered an honorarium of £500 which the complainant thought was quite exorbitant for a 6 hour session, plus travel and accommodation if required.

The complainant stated that he was not a leading expert in parathyroid or bone disease and had not published in this area. It appeared that the invitation had been sent out using a generated list of recipients. The complainant had received two copies, one was blank and not even signed.

The Panel had some concerns about the arrangements. It queried whether the invitation was sufficiently clear that the honorarium offered was a payment for work and advice. It did not appear that invitees had been sent the agenda with the invitation. The agenda provided by Abbott was headed Zemplar UK Advisory Board Meeting compared with the invitation provided by the complainant which was headed Abbott Renal Care Advisory Board. The agenda showed only two breakout sessions each of an hour (including feedback and conclusions). Most of the rest of the day was taken up with various presentations lasting a total of just over two hours and a total of 45 minutes for questions. The Panel queried whether the 6 hour meeting allowed enough time for feedback and input from the attendees such that each would contribute sufficient to justify the honorarium. There was less than three hours during the day when delegates were not listening to set presentations. It did not appear that delegates were expected to do any preparation for the meeting.

On balance the Panel considered that the arrangements were such that the meeting was not an advisory board but a promotional meeting. It was not appropriate to pay doctors to attend such meetings. High standards had not been maintained; breaches of the Code were ruled.

On balance the Panel did not accept that the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure; the delegates to the meeting had been expected to do some work, no breach of Clause 2 was ruled.

Upon appeal by Abbott the Appeal Board noted that the purpose of the meeting was to determine whether the current positioning of Zemplar as a first line choice was appropriate. The Appeal Board was concerned that the agenda was very full of formal presentations and the time available for discussion might be limited. However, on balance it considered that the invitation and agenda sent to the complainant together with the arrangements for the advisory board were not unreasonable. Participants were being paid to attend an advisory board not a promotional meeting. No breach of the Code was ruled.

The Appeal Board noted that Abbott had intended to hold the advisory board with a maximum of fifteen renal physicians. On 21 September twenty one invitations were sent. By 25 October only two physicians had confirmed their attendance. Abbott submitted that due to the low uptake, and in order to ensure that the meeting could take place in central London as planned, the company started to concentrate on inviting local experts. A further thirty five invitations were generated in head office and distributed by Abbott's representatives. Abbott's representatives could suggest names of invitees but these were assessed and invited by head office.

The Appeal Board was concerned that the list of invitees provided by Abbott had consisted of seventy five names and not fifty-six (21 plus 35) as stated. Despite being assured by Abbott's representatives at the appeal that only those on the list were invited, the list did not include the complainant's name. Neither of the invitations supplied by the complainant were on company headed paper, his name had been hand written on one and both were unsigned. At the appeal hearing Abbott's representatives were unable to explain this discrepancy. The company did not know the name of the complainant. The Appeal Board was concerned that sales representatives appeared to have been involved in issuing invitations without head office's knowledge. The Appeal Board considered that the process for inviting attendees was disorganised and in that regard high standards had not been maintained; the Appeal Board upheld the Panel's ruling of a breach of the Code

A consultant physician complained about an invitation from Abbott Laboratories Limited to attend a renal care advisory board. The company had offered an honorarium of £500 plus travel and accommodation if required.

COMPLAINT

The complainant was a nephrologist and physician and stated that he was not a leading expert in parathyroid or bone disease, and an honorarium of £500 looked to him quite exorbitant for a 6 hour session. He had not

published in this area. For a busy and genuine expert with detailed expertise, perhaps it could be justified better.

It appeared that the invitation had been sent out using a generated list of recipients. The complainant had received two copies, one was blank and not even signed. None of these generated confidence that it was intended as a genuine device to guide clinical use.

The reason behind the invitation looked suspiciously like commercial promotion, or at least a kind of marketing focus group for directing sales tactics, not genuine consultation on clinical management as claimed.

When writing to Abbott the Authority asked it to respond in relation to Clauses 18.1, 9.1 and 2.

RESPONSE

Abbott stated that the invitation was sent to consultant nephrologists only, whom Abbott wished to employ as consultants, in order to gain the benefit of their expertise on a number of issues relating to its product, Zemplar (paricalcitol). These issues were outlined in the enclosed 'Group Consulting Program Proposal Form' used when this meeting was formally approved, in line with the Code. They were as follows:

- To gain feedback from advisors on the latest data on vitamin D receptor analogues (VDRAs) and secondary hyperparathyroidism (sHPT) in chronic kidney disease (CKD).
- To gain feedback from the advisors on the use of paricalcitol in the UK with regard to value, its inclusion in formularies, and their perception of the data presented.
- To obtain feedback from the advisors on positioning paricalcitol in the UK market with regard to the prevention and treatment of sHPT associated with chronic renal failure.

In order to best meet these aims, Abbott invited consultant nephrologists experienced in treating sHPT. The company hoped to gain a UK perspective on the impact of key data on the treatment paradigms involved in managing sHPT. This was why Abbott invited the nephrologists it did, rather than targeting the more academic or influential clinicians, who might have published data in this area.

The meeting to which the complainant had been invited was the only such meeting. It was useful to try and gain input from a number of different geographic regions and so renal physicians from throughout the country were invited. The company approved a maximum of 15 to attend. This was considered to be an appropriate number in order to best facilitate constructive discussions in breakout groups to discuss some of the key issues raised as set out on the agenda.

On 21 September, 21 invitations were distributed. Unfortunately, Abbott had only received confirmation of attendance from two of the invitees by 25 October. As a result, a further 35 invitations were distributed, throughout the UK (although mainly to physicians based in London, due to the location for this meeting). At the time of writing this response, 11 attendees had confirmed and apologies had been received from another five.

The honorarium for each of the attendees was £500. As this meeting was 6 hours long, Abbott considered this was appropriate reimbursement (£83.33/hour). The BMA Fee Guidance Schedule included a section on payment for work for pharmaceutical companies. It did not provide specific guidance on advisory boards but recommended an hourly rate of £216.50 for participation in clinical trials, and up to £103/hour for completion of a medical research questionnaire. Taking this guidance into account, Abbott did not consider that the honorarium was excessive. The offer to reimburse for accommodation and travel cost was to cover any additional subsistence expenses incurred by physicians based outside London.

A list of invitees (including their place of work) was provided. A copy of the draft agenda (and associated slides) was also provided. These were currently undergoing internal approval and might change slightly as part of this approval process.

There was also to be three clinical presentations delivered on the day, only one of which would be from an Abbott employee. The Abbott presentation, covering health economic data would be approved before the meeting but was not yet finalised. Two guest speakers, nephrologists with considerable expertise in the area, had been verbally briefed on the topics they were expected to cover. The Zemplar medical advisor would be meeting them on the morning of the meeting to review their slides and ensure that they were consistent with the brief. Abbott did not yet have these slides to hand.

PANEL RULING

The Panel considered that there was a difference between holding a meeting for health professionals and employing them to act as consultants. It was acceptable for companies to arrange advisory board meetings and the like and to pay health professionals and others for advice on subjects relevant to the products they promoted. Nonetheless the arrangements for such meetings had to comply with the Code. The requirements as to hospitality being of a reasonable standard etc, as set out in Clause 19 of the Code had to be followed. The company must be able to justify the number of meetings held. The choice and number of delegates should stand up to independent scrutiny; each should be chosen according to their expertise such that they would be able to contribute meaningfully to the purpose and expected outcomes of the meeting. The number of delegates at a meeting should be limited so as to allow active participation by all. The agenda must allow sufficient time for feedback and input by the delegates. Invitations to participate in an advisory board meeting should clearly state the purpose of the meeting, the expected role of the invitees and the amount of work to be undertaken; it should be clear that any honorarium offered was a

payment for such work and advice.

The Panel had some concerns about the arrangements. It queried whether the invitation was sufficiently clear that the honorarium offered was a payment for work and advice. It did not appear that invitees had been sent the agenda with the invitation. The agenda provided by Abbott was headed Zemplar UK Advisory Board Meeting compared with the invitation provided by the complainant which was headed Abbott Renal Care Advisory Board. The agenda showed only two breakout sessions each of an hour (including feedback and conclusions). Most of the rest of the day was taken up with various presentations lasting a total of just over two hours and a total of 45 minutes for questions. The Panel queried whether the 6 hour meeting (10am – 4pm) allowed enough time for feedback and input from the attendees such that each would contribute sufficient to justify an honorarium of £500. There was less than three hours during the day when delegates were not listening to set presentations. This would, in effect only give each delegate assuming 15 attended, less than 12 minutes each in which to contribute to the proceedings. It did not appear that delegates were expected to do any preparation for the meeting.

On balance the Panel considered that the arrangements for the meeting meant that it was not an advisory board but a promotional meeting. It was not appropriate to pay doctors to attend such meetings. The Panel ruled a breach of Clause 18.1 of the Code. High standards had not been maintained; a breach of Clause 9.1 was ruled.

On balance the Panel did not accept that the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure; the delegates to the meeting had been expected to do some work, no breach of Clause 2 was ruled.

APPEAL BY ABBOTT

Abbott submitted that the meeting was a bona fide advisory board, in line with the Authority's guidance. Abbott noted that the Panel had queried whether the invitation was sufficiently clear that the honorarium offered was a payment for work and advice.

Abbott submitted that the invitation informed all potential advisors of the exact nature of the meeting and what Abbott expected from them in return for the honorarium detailed therein.
The relevant section of the invitation read:

'The main objectives of the advisory board are:

- To gain feedback from advisors on the latest data on VDRAs and sHPT in CKD
- To gain feedback from the advisors on the use of paricalcitol in the UK with regard to value, its inclusion in formularies and their perception of the data presented
- To obtain feedback from the advisors on positioning paricalcitol in the UK market with regard to the prevention and treatment of sHPT associated with chronic renal failure.

During the meeting there will be breakout sessions where you will be asked to comment on the data and discuss the relevance to the treatment of sHPT in the UK. In addition to that, you will be advising Abbott on the positioning of paracalcitol for the treatment of sHPT.

An honorarium of £500 will be paid to each participant'.

Abbott submitted that the invitation was thus clear as to the expected role of the participants.

Abbott noted that the Panel had observed that the agenda it had provided was headed Zemplar UK Advisory Board Meeting compared with the invitation provided by the complainant headed Abbott Renal Care Advisory Board. Abbott submitted that it had carefully worded the invitation in order to strike a balance between providing adequate information about the nature of the meeting, whilst ensuring that it did not constitute a promotional mailing. With this balance in mind Abbott chose not to mention Zemplar. The invitation did, however, make it quite clear – as discussed above - that the meeting was an advisory board around paricalcitol, that the attendees were being invited in an advisory capacity, that they would be expected to contribute actively and that Abbott was expecting advice from all attendees, relating to the key objectives outlined in the invitation.

Abbott noted that the Panel queried whether the 6 hour meeting allowed enough time for feedback and input from the attendees such that each would contribute sufficient to justify an honorarium of £500. Abbott submitted that the meeting included two group breakout sessions. In each breakout session attendees divided into two smaller groups to facilitate open, interactive discussion, thus ensuring the opportunity for all advisors to adequately voice their opinions relating to the key objectives of the meeting. It appeared that this was not taken into consideration in the Panel's deliberations. The Panel also commented on the proportion of the day spent on presentations. Expert interactive presentations of data served two important functions during company advisory boards. Firstly they ensured that the participating advisors had seen the appropriate data to participate fully in the meeting; unfortunately advisors did not always give pre-reading the time and energy needed to achieve this. Secondly and importantly, observing reactions to and understanding of the data could form an important part of the value of such meetings to the company. It should be noted that every session of the meeting was interactive, with the advisors' views solicited throughout. The honorarium was intended to reimburse the time taken to attend the meeting as a whole, rather than just to cover time spent on breakout sessions. It would be unreasonable to expect consultant physicians to attend a meeting of this nature and not reimburse them for its entire duration. Even subtracting the hour spent on breaks the honorarium was in line with the market and BMA rates.

In view of the above, Abbott submitted that the Panel was incorrect to conclude that this was a promotional

meeting. Abbott maintained that this advisory board was in line with Authority's guidance on advisory boards and that the size of the honorarium was commensurate with the time spent in ensuring that this meeting fulfilled the stated objectives. Abbott therefore denied breaches of Clauses 18.1 and 9.1 of the Code.

COMMENTS FROM THE COMPLAINANT

The complainant stated that after reading Abbott's appeal the basis of his complaint remained intact. The complainant was not an expert in renal osteodystrophy, it had never been his interest, nor had he published in this field. So to invite him to share in a consultation in this way still looked like product promotion under the guise of seeking an expert opinion, flattering to the recipient though that might seem. Whether the remuneration was appropriate either for direct promotion or for marketing advice or for expert consultation was not the primary issue – it was the apparent deceit inherent in the invitation that the complainant found disturbing and inappropriate.

* * * * *

During its consideration of the case and before reaching a ruling but after Abbott's representative's had left the room the Appeal Board noted that on examination of the file copy of the complaint a representative's business card was attached to the invitation supplied by the complainant. The Appeal Board had not previously been given a copy of the business card as Abbott had not been told of the representative's involvement for fear of identifying the complainant who wished to remain anonymous.

* * * * *

APPEAL BOARD RULING

The Appeal Board noted from the Abbott representatives that the purpose of the meeting was to determine whether the current positioning of Zemplar as a first line choice was appropriate. The Appeal Board was concerned that the agenda was very full of formal presentations and the time available for discussion might be limited. However, on balance the Appeal Board considered that the invitation and agenda sent to the complainant together with the arrangements for the advisory board were not unreasonable. Participants were being paid to attend an advisory board not a promotional meeting. The Appeal Board ruled no breach of Clause 18.1 of the Code. The appeal on this point was successful.

The Appeal Board noted that Abbott had intended to hold the advisory board with a maximum of fifteen renal physicians. On 21 September twenty one invitations were sent. By 25 October only two physicians had confirmed their attendance. The Abbott representatives submitted that due to the low uptake, and in order to ensure that the meeting could take place in central London as planned, the company started to concentrate on inviting local experts. A further thirty five invitations were generated in head office and distributed by Abbott's representatives. Abbott's representatives could suggest names of invitees but these were assessed and invited by head office.

The Appeal Board was concerned that the list of invitees provided by Abbott had consisted of seventy five names and not fifty-six (21 plus 35) as stated by Abbott in its response to the Panel. Despite being assured by Abbott's representatives at the appeal hearing that only those on the list were invited, the list did not include the complainant's name. Neither of the invitations supplied by the complainant were on company headed paper, his name had been hand written on one and both were unsigned. At the appeal hearing Abbott's representatives were unable to explain this discrepancy. The company did not know the name of the complainant. The Appeal Board was concerned that sales representatives appeared to have been involved in issuing invitations without head office's knowledge. The Appeal Board considered that the process for inviting attendees was disorganised and in that regard high standards had not been maintained; the Appeal Board upheld the Panel's ruling of a breach of Clause 9.1. The appeal on this point was unsuccessful.

Complaint received	**31 October 2007**
Case completed	**30 January 2008**

GENERAL PRACTITIONER v ROCHE

Conduct of a representative

A general practitioner complained that a representative from Roche had offered to provide a Christmas lunch for his primary care team. The complainant alleged that this would constitute sponsorship of a meeting wholly of a social nature.

An email sent to the complainant by the practice manager of another practice in the same building stated '…, the Roche rep, has offered to provide a Christmas lunch …. Although I know what your stance is on reps, the invitation is also open to you and your team if you want. If you could let me know …'.

The Panel noted Roche's submission that the meeting was planned as a promotional meeting and the representative had not referred to it as a 'Christmas lunch'. The representative's call notes did not refer to Christmas lunch. The only reference to Christmas lunch was in the email sent from the practice manager to the complainant. It appeared that it was this email which had prompted the complaint.

It was difficult in cases like this when there was a discrepancy between the parties. On the information before it the Panel considered that there was no evidence that the Roche representative had offered to provide Christmas lunch as alleged. Thus no breach of the Code was ruled.

A general practitioner complained about the conduct of a representative from Roche Products Limited.

COMPLAINT

The complainant stated that the representative had offered to provide a Christmas lunch for his primary care team. The complainant alleged that this would constitute sponsorship of a meeting wholly of a social nature in breach of Clause 15.3 of the Code.

An email sent to the complainant by the practice manager of another practice in the same building stated '…, the Roche rep, has offered to provide a Christmas lunch for the PHCT on the 19th December. Although I know what your stance is on reps, the invitation is also open to you and your team if you want. If you could let me know and I can let [the representative] know approximate numbers'.

When writing to Roche, the Authority asked it to respond in relation to Clauses 2, 9.1, 15.2 and 19.1 in addition to Clause 15.3 cited by the complainant.

RESPONSE

Roche explained that the complainant worked in one of two practices that shared a primary care centre. Although the two practices acted separately they shared some parts of the building, eg meeting rooms and library.

The representative had good working relationships with some customers in the other practice and in late October/early November he approached the practice manager about conducting a promotional lunch meeting for the practice. It was made clear that the intent would be to promote with approved materials and provide an appropriate buffet lunch. He was given the date of 19 December (lunchtime) for the meeting and expressed that all health professionals in the building, including the complainant's practice, would be welcome to attend.

Approximately one week later the practice manager telephoned the representative to tell him that he could no longer do the lunch as a member of the neighbouring practice had objected on the grounds that his practice did not entertain members of the pharmaceutical industry. Subsequently, the meeting was cancelled.

The following email was sent by the practice manager in response to a request from Roche to assist with this investigation:

'This is to confirm that a lunchtime meeting was arranged between myself and [the representative] in respect of Bonviva. It was expected that [the representative] would be bringing promotional material on Roche products to the meeting for discussion with the GPs, practice nurse and district nurses in attendance. If you require any further clarification please do not hesitate to get in touch with me.'

The representative intended to conduct a meeting that was in keeping with the company's standard operating procedures (SOPs) regarding promotional meetings, and most importantly, a meeting that was in keeping with the Code as regards promotional meetings. Roche therefore denied any breach of the Code. Roche took all accusations seriously and would nonetheless ensure that all representatives were reminded of their obligations under the Code with respect to meetings of this type.

In response to a request from the Panel for further information Roche provided relevant records from its call recording database.

Two elements of free text were recorded on the database. One was a general call note, the other was specific to Bonviva promotion.

- In a face-to-face call on 11 October the

representative's call notes read: 'discussed in-house educational on osteoporosis/ to call back in 2 weeks'. The Bonviva notes read 'discussed appt with key doc/plan to call back in 2 weeks to confirm date for in-house meeting'.

- Following this, a face-to-face call on 1 November, call notes read 'discussed in-house meetings plan, meeting booked for Dec'. The Bonviva notes read: 'meeting booked for Dec'.

- The final call notes on 6 November read: 'meeting cancelled in Dec / no current plans to hold clinical meetings in centre'. The Bonviva notes read: 'no Bonviva usage as yet'.

In relation to the discrepancy between Roche's response and the complainant's perspective, Roche stated that the representative confirmed he offered to conduct a promotional meeting and suggested a date around the Christmas period. He stated that he did not under any circumstances refer to the meeting as a 'Christmas lunch'. It was presumed there was a possibility that the practice manager was the one who had referred to it as 'Christmas lunch' in her email to the complainant's practice. Naturally Roche had no control over the content and context of her emails. If further clarity was required, the Authority might wish to contact the practice manager who was happy to provide information.

PANEL RULING

The Panel noted Roche's submission that the meeting was planned as a promotional meeting and the representative had not referred to it as a 'Christmas lunch'. The representative's call notes did not refer to Christmas lunch. The only reference to Christmas lunch was in the email sent from the practice manager to the complainant. It appeared that it was this email which had prompted the complaint.

It was difficult in cases like this when there was a discrepancy between the parties. On the information before it the Panel considered that there was no evidence that the Roche representative had offered to provide Christmas lunch as alleged. Thus no breach of Clauses 2, 9.1, 15.2, 15.3 and 19.1 was ruled.

Complaint received	**13 November 2007**
Case completed	**10 January 2008**

CASE AUTH/2067/11/07

JOHNSON & JOHNSON CONSUMER SERVICES EAME v PFIZER

Smoking cessation campaign

Johnson & Johnson Consumer Services Eame alleged that Pfizer's 'Serious Quitters' smoking cessation campaign constituted the indirect promotion of Champix (varenicline), a prescription only medicine, to the public. The use of expressions such as 'new ways for you to quit' in conjunction with the suggestion to '… visit your local NHS stop smoking service or GP…' clearly told the patient that a new treatment for smoking cessation was available via a smoking cessation service or GP. Johnson & Johnson noted that television and radio advertisements placed an audible emphasis placed on the word 'new'. Champix, launched in December 2006, was the only treatment that could currently be considered as new. Johnson & Johnson added that by advising readers to seek advice from a smoking cessation clinic or GP was likely to bias treatment towards prescribed treatments such as Champix; patients were not told that there were treatments available over the counter.

The Panel noted Pfizer defined a serious quitter as a smoker who was motivated to quit despite having failed at least once before. Further the campaign aimed to *inter alia* highlight the important role of the health professional in helping smokers to quit.

The Panel considered that Pfizer's campaign in recommending visiting the local stop smoking service or GP practice to find new ways to quit might imply that there was some new approach to assist stopping smoking. In each press advertisement the word 'new' was used three times; it was not clear that the word related to previously untried ways for the individual as submitted by Pfizer. In any event the potential quitter would paraphrase the statement and ask about new ways to quit which might lead to health professionals and smoking cessation advisers to only consider new treatments. The most recent treatment was Champix, a prescription only medicine. Support, advice and NRT would be available from community pharmacists (including those who were not smoking cessation advisers) and these were not mentioned despite Pfizer's submission that the campaign aimed to highlight the role of the health professional.

The campaign encouraged smokers to discuss treatment options with certain health professionals only. The materials would encourage smokers to ask about new treatments. The health professional was likely to associate the word 'new' only with Champix and thus prescribe that product. The Panel considered that in effect the material encouraged patients to ask for a specific prescription only medicine to be prescribed. A breach of the Code was ruled.

The Panel did not consider that the emphasis in the campaign on the word 'new' meant that the campaign constituted advertising of a prescription only medicine to the public. No breach of the Code was ruled.

Johnson & Johnson Consumer Services Eame Limited complained about the 'Serious Quitters' smoking cessation campaign by Pfizer Limited.

COMPLAINT

Johnson & Johnson stated that it did not have issue with Pfizer's campaign per se but it had specific concerns about the use of the expressions 'new ways for you to quit/new ways to help you quit smoking and stay quit' eg:

Television campaign [Channel 5, 1 October 2007]: 'Whatever your reason for wanting to quit smoking, visit your local NHS stop smoking service or GP practice about new ways for you to quit. The moment you ask could be the moment you stop.'

Radio campaign [Kiss FM, 8 October 2007]: 'Whatever your reason for quitting, visit your local stop smoking service or GP practice to find out about new ways for you to quit, The moment you ask could be the moment you stop.'

Press campaign [Daily Express, 30 July 2007]: '… ask your healthcare professional about new ways to help you quit smoking and stay quit.' The items signed off with the statement 'Serious Quitters seek new ways to quit'.

Johnson & Johnson noted that Clause 20.2 of the Code stated that: 'Statements must not be made for the purpose of encouraging members of the public to ask their health professional to prescribe a specific prescription only medicine'. The supplementary information to Clause 20.2 Information to the Public stated: 'A company may conduct a disease awareness or public health campaign provided that the purpose is to encourage members of the public to seek treatment for their symptoms while in no way promoting the use of a specific medicine'. Disease awareness campaigns (DACs) were also covered in detail in the 'Disease Awareness Campaign Guidance – Medicines and Healthcare products Regulatory Agency (MHRA) Guidance Note Number 26'. This document was published in 2003 and was referenced in the supplementary information to Clause 20.2. The MHRA disease awareness guidance stated 'Campaigns which aim to stimulate demand by the public for a specific medicine or specific medicines are likely to be

considered promotional, falling within the scope of Title VIII of Directive 2001/83/EC'. The document went on to state: 'A DAC may make reference to the availability of treatment options (which may include medicines as part of a range of possible management options) but should not be of such a nature that an individual would be encouraged to approach a prescriber to request a particular medicinal option. The emphasis of the material should be on the condition and its recognition rather than on the treatment options'. In addition, the guidance stated that DACs should include information that was, *inter alia*, 'balanced and fair'. In particular, it stated that 'Management options should be presented in a balanced and fair manner that does not unduly emphasize particular options or the need to seek treatment'.

In Johnson & Johnson's view, the reference to '… new ways for you to quit' in conjunction with the suggestion to '… visit your local NHS stop smoking service or GP practice…' clearly told the patient that a new treatment for smoking cessation was available via a smoking cessation service or GP. Johnson & Johnson also noted that there was an audible emphasis placed on the word 'new' on both the television and radio advertisements. The only treatment for smoking cessation that could currently be considered new was Pfizer's product Champix (varenicline) which was launched in December 2006.

Furthermore, the recommendation to seek advice on new treatment options from a smoking clinic or GP failed to cover the full range of established treatment options that were available widely through a number of types of retail outlets. In the case of nicotine replacement therapy (NRT), for instance, products were available as both GSL and pharmacy products. A recommendation to seek advice from a smoking cessation service or GP was likely to bias treatment towards prescribed treatments such as Champix.

In intercompany correspondence (provided), Pfizer had explained that its campaign was known as 'Serious Quitters'. It then defined a serious quitter as a smoker who was motivated to attempt to quit smoking but had failed in at least one previous attempt. Pfizer suggested that its campaign was targeted at these quitters in order to maintain their motivation and continue to encourage them to seek new ways to quit.

Johnson & Johnson argued that not only quitters who had already tried to stop smoking could be considered as serious quitters. Further, it was not clear in any of the components mentioned above that the campaign was targeted only at those smokers who had tried to quit before; the campaign would reach all smokers including those who had not previously tried to quit. Finally, even if this campaign communicated only to smokers who had previously tried to quit, this would not negate the overall impression that smokers were being asked to seek advice on a new form of treatment for nicotine addiction.

Pfizer argued that the phrase 'new ways for you to quit' sought to tell the reader that there were new ways for them to quit because there would be methods that they had not tried. Johnson & Johnson did not accept that this was the overall impression given. If Pfizer had wished to provide an entirely balanced view of current therapy options it could have suggested in its campaign that smokers contact a health professional such as a GP, smoking cessation service or pharmacist for information.

Johnson & Johnson maintained that the overall impression of the Serious Quitters campaign was that there was a new option available from the smoker's GP or smoking cessation service. The only new option currently available was Pfizer's product Champix. Johnson & Johnson therefore believed that this campaign constituted the indirect promotion of a prescription only medicine to the general public in breach of Clauses 20.1 and 20.2.

RESPONSE

Pfizer stated that the campaign was developed in accordance to MHRA guidance on DACs and internal standard operating procedures and in consultation with an independent charity that aimed to help people stop smoking. The campaign was launched in collaboration with the charity.

Pfizer defined 'serious quitter' as a smoker who was motivated to attempt to quit but had failed in at least one previous attempt. There was of course no standard definition that accurately defined what made a 'serious quitter' and every company would have its own interpretation. Smoking was the leading preventable cause of death in the UK (over 114,000 deaths per year) and was a very difficult addiction to overcome. It was therefore important for those attempting to quit to maintain their motivation and to continue to seek new ways to do so. Most smokers tried to quit five to seven times before they finally succeeded and only 3-5% of unaided quitters remained smoke free after 6-12 months. This was why Pfizer's campaign aimed to reach all smokers in general and serious quitters in particular. Pfizer did not consider that its definition of 'serious quitters' nor the breadth of the campaign's reach breached the Code.

Pfizer did not believe that the wording implied or encouraged a prescription of Champix and it strongly believed that its campaign represented a fair and balanced view of all current treatments available to the serious and motivated quitter for the following reasons:

The phrase 'new ways for you to quit' sought to communicate that there were new ways for an individual smoker to quit because there would be methods that they had not yet tried. For example, a quitter might have used counselling support but not yet tried NRT. For that individual, NRT would be 'new'. New ways for a serious quitter could therefore mean counselling or behavioural therapy, or a variety of medicines including the many different forms of NRT, Zyban, Champix or other options. The majority of smokers tried to quit with no help at all, and this was the least effective method.

The options available to help a smoker quit were reinforced on the Serious Quitters website (www.seriousquitters.co.uk) which discussed the different types of medicines available (without naming specific products) as well as behavioural therapy in the 'know your options' section.

Pfizer had deliberately used the phrase 'new ways for you to quit' in the plural so that it pointed towards different options that were available to the serious quitter who was looking for ways that were new to him or her. This could be any psychological or pharmacological treatment that they had not tried before. Pfizer did not believe that this implied Champix.

The campaign aimed to: demonstrate the health benefits of quitting; highlight the important role of the health professional in helping smokers quit successfully and provide further support to smokers who were serious about quitting for good. The campaign had been prepared fully in accordance with MHRA guidance and therefore fell outside the scope of the prohibitions set out in Title VIII of Directive 2001/83/EC.

The relevant requirements set out in the guidance were:

- The Serious Quitters campaign focussed on promoting awareness and educating the public about health, disease and its management, as highlighted in Point 2 of the guidance.

- Point 3 of the guidance stated that DACs should highlight to the public where they could find appropriate sources of advice. The Serious Quitters campaign did this clearly by advising smokers to visit their NHS Stop Smoking Service or GP practice. This would normally result in discussions with pharmacists, nurses, stop smoking advisers or GPs, depending on the service.

- Point 4 of the guidance stated that campaigns which aimed to stimulate the public to demand a specific medicine or specific medicines were likely to be considered promotional. Serious Quitters was a public health awareness campaign which aimed to demonstrate the benefits of quitting, highlighted the important role of the health professional in helping smokers to quit successfully and provided further support for smokers who were serious about quitting for good. It did not promote any prescription or non-prescription medicines.

- Point 5 of the guidance stated that a DAC might refer to the availability of treatment options (which might include medicines as part of a range of possible management options) but not in such a way as to encourage an individual to ask a prescriber to prescribe a particular medicine. Serious Quitters communicated to the smoker that if they had not found a way to quit that worked for them, they should visit their NHS Stop Smoking Service or GP practice. Visiting NHS Stop Smoking Services might involve assessment by specialist stop smoking advisers, pharmacists providing a smoking cessation service, nurse advisers or GPs. They played a key role in helping serious quitters to stop smoking, as well as helping them find psychological or pharmacological therapies (prescription or non-prescription) that they had not tried before.

- Point 6 of the guidance stated that DACs for diseases or conditions where there was only one, one leading, or few medicines, could potentially draw attention to the medicine (albeit indirectly), regardless of whether it was referred to or not. DACs in these circumstances required particular care. There were a wide range of treatment options (not one, one leading, or a few) available to the smoker who had tried before to quit but failed, such as various forms of NRT, behavioural modification therapies and prescription treatments. Therefore, the DAC did not draw attention to one particular treatment.

- Point 7 of the guidance stated that DACs should include information that was:

i) Accurate: The information provided by the Serious Quitters campaign regarding the health benefits of quitting was accurate and was not misleading. It was widely accepted that quitting smoking was one of the best ways to improve health.

ii) Up-to-date: The Serious Quitters campaign was launched in collaboration with a charity. Callers to Serious Quitters had the option of being transferred to a charity counsellor. The information obtained by the smoker from the charity counsellor would be the most up-to-date information available. Charity counsellors were experts in their field and provided accurate independent information to smokers who were trying to quit.

iii) Substantiable: Good advice from a health professional, together with support strategies and treatments, were crucial factors in helping smokers beat nicotine addiction. Studies showed that even brief advice from health professionals increased the likelihood of a smoker staying off cigarettes by up to 30%. This was why serious quitters were recommended to seek help from health professionals; without their advice and support, the chances of quitting were considerably lower.

iv) Comprehensive: The health aspects of smoking were well known to the public and the benefits of stopping smoking were highlighted in the campaign through statements such as 'your lungs will love you for it' and 'your tongue will love you for it'. The many health benefits from stopping smoking were reinforced on the Serious Quitters website in the 'know the reasons why' section.

v) Balanced and fair: It was well accepted that smoking was unhealthy and the campaign sought to communicate the health benefits to be gained from quitting. The campaign also communicated specifically with those smokers who had tried to quit before and

failed. Therefore it recommended that they visit their NHS stop smoking service or GP practice for support and advice on new ways for them to quit. It did not however promote any particular treatment.

vi) Readable and accessible: The language, design and formatting of the campaign materials had all been prepared so as to be clearly understood by the intended audience ie smokers who were serious about quitting.

vii) Source identified: There were no medical claims in the campaign materials that required supporting references to be displayed. The key principles which the campaign sought to communicate were supportable by clinical literature as outlined above. The provision of the campaign by Pfizer in collaboration with the charity was clearly documented.

• Point 8 of the guidance stated that the campaign must meet the DAC guidance on structure set out in the 'Advice for the patient' section. The campaign highlighted to the serious quitter that if they had tried to quit before and failed, they should visit their local NHS Stop Smoking Service or GP practice to find out about new ways for them to quit. Further support and advice was available via the website together with a freephone telephone number so that the serious quitter could call an expert smoking cessation counsellor from the charity.

It was for the reasons above that Pfizer believed that it had fully met the criteria set out in the MHRA guidance for DACs by highlighting the importance of stopping smoking and the availability of treatment options for the serious quitter. Pfizer believed that the Serious Quitters campaign complied in all respects with Title VIII of Directive 2001/83/EC (the 'Advertising Directive') as implemented in the UK by the Medicines (Advertising) Regulations 1994 and with the Code. Accordingly, Pfizer denied a breach of Clauses 20.1 and 20.2. In Pfizer's view its campaign provided high quality, non-promotional information and did not encourage members of the public to ask their health professional to prescribe a specific prescription only medicine.

PANEL RULING

The Panel noted that it had to rule with regard to the Code and not whether or not the materials were in line with the MHRA guidance.

The Panel noted that in accordance with Clause 20.2 of the Code companies could make information about prescription only medicines available to the public either directly or indirectly. Such information must be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Further, statements must not be made for the purpose of encouraging members of the public to ask their health professional to prescribe a specific prescription only medicine.

The supplementary information to Clause 20.2 stated that in relation to DACs that particular care must be taken where the company's product, although not named, was the only medicine relevant to the disease or symptoms in question. DACs or public health campaigns could be conducted with the purpose of encouraging the public to seek treatment while in no way promoting the use of a specific medicine.

The Panel noted Pfizer defined a serious quitter as a smoker who was motivated to attempt to quit but had failed in at least one previous attempt. Further the campaign aimed to *inter alia* highlight the important role of the health professional in helping smokers to quit.

The Panel considered that Pfizer's campaign in recommending readers to visit the local stop smoking service or GP practice to find new ways to quit might imply that there was some new approach to assist stopping smoking. In each press advertisement the word 'new' was used three times; it was not clear that the word related to previously untried ways for the individual as submitted by Pfizer. In any event the potential quitter would paraphrase the statement and ask about new ways to quit which might lead to health professionals and smoking cessation advisers to only consider new treatments. The most recent treatment was Pfizer's product Champix which was a prescription only medicine. Support, advice and NRT would be available from community pharmacists (including those who were not smoking cessation advisers) and these were not mentioned despite Pfizer's submission that the campaign aimed to highlight the role of the health professional.

The campaign encouraged smokers to discuss treatment options with certain health professionals only. The nature of the materials would encourage smokers to ask about new treatments. The health professional was likely to associate the word 'new' only with Champix and thus prescribe that product. Thus the Panel considered that in effect the material encouraged patients to ask for a specific prescription only medicine to be prescribed. A breach of Clause 20.2 was ruled.

The Panel did not consider that the emphasis in the campaign on the word 'new' meant that the campaign constituted advertising of a prescription only medicine to the public. No breach of Clause 20.1 was ruled.

Complaint received 21 November 2007

Case completed 31 January 2008

CASE AUTH/2068/11/07

BAYER SCHERING PHARMA v MERCK SERONO

Hospitality at international meeting

Bayer Schering Pharma complained that, at an international meeting held in Prague in October 2007, Merck Serono had accommodated its UK sponsored delegates at a 5 star hotel in the city centre.

Bayer Schering stated that the hotel was a member of the internationally recognised luxury hotel brand 'Leading Hotels of the World' (LHW). The opening page of the hotel website described staying there as 'a unique experience of classical elegance and sparkling luxury' and that 'The [hotel] belongs to one of the most luxurious hotels and its clients expect individual top quality service and fulfilment of each single wish'.

Additionally, the LHW website emphasised the luxury and first class service provided by its member hotels.

Whilst the Code did not give a star rating or any other specific criteria that would define 'deluxe', in Bayer Schering's view, the hotel's 5 star rating and membership of the LHW confirmed that it would inevitably be perceived as a 'deluxe' venue and thus its use for hospitality was not acceptable under the Code.

The Panel noted that the Code stated that the costs of hospitality must not exceed that level which recipients would normally adopt when paying for themselves. Supplementary information stated that hospitality was limited to refreshments/subsistence (meals and drinks), accommodation, genuine registration fees and the payment of reasonable travel costs which a company might provide to sponsor a delegate to attend a meeting. The supplementary information further stated that lavish and deluxe venues must not be used and that the impression that was created by the arrangements for any meeting must always be kept in mind. It should be the programme that attracted delegates and not the associated hospitality or venue. The Code did not prohibit the use of five star hotels per se. Some companies' own codes and policies prevented use of such hotels.

The Panel noted that Merck Serono's invitation to attend the meeting in Prague had not named the hotel and so in that regard delegates could not have been attracted to the meeting by the accommodation being offered. The hotel was convenient for the meeting venue and according to Merck Serono accommodation was limited. Nonetheless, accommodation had been provided at an hotel which was a member of the LHW group and more often than not rated five star and consistently described in terms of the luxury it provided, not only on its own website but also on others. Even allowing for differences in the star rating system, the impression was thus that Merck Serono's guests were being accommodated in a luxury hotel. The final breakdown of costs showed that one night's bed and breakfast accommodation cost £238 per person.

The Panel noted that almost half of Merck Serono's sponsored delegates were nurses. In the Panel's view the cost of accommodation was more than most people might be expected to pay if they were paying for themselves; it was higher than nurses would normally pay.

On balance, the Panel considered that excessive hospitality had been provided and a breach of the Code was ruled.

Bayer Schering Pharma complained about hospitality provided by Merck Serono to UK health professionals at an international meeting in Prague.

COMPLAINT

Bayer Schering sought clarification of Clause 19.1 of the Code with respect to the activities of Merck Serono at the recent meeting of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) held from 10-14 October in Prague. Whilst at the meeting, Bayer Schering became aware that Merck Serono had accommodated its UK sponsored delegates at a 5 star hotel in the city centre.

The hotel was a member of the internationally recognised luxury hotel brand 'Leading Hotels of the World' (LHW). A brochure for the hotel was provided. The opening page of the hotel website described staying there as 'a unique experience of classical elegance and sparkling luxury' and that 'The [hotel] belongs to one of ***the most luxurious hotels*** and its clients expect individual top quality service and fulfilment of each single wish'.

Additionally, the LHW website stated that: 'The Leading Hotels of the World understands the finer points of hospitality and luxury. Indulge yourself in a lifestyle of luxury at one of our 5 star hotels and the unparalleled comfort they offer. The Leading Hotels of the World's featured hotels cater to the discriminating few, where first class service is a norm rather than an exception. The Leading Hotels of the World features small luxury hotels, resort hotels as well as world-renowned stately hotels offering all the possibilities for family getaways, romantic escapades and business meetings. Whether you need accommodation for business or pleasure, The Leading Hotels of the World will have the perfect solution for you'.

Whilst Clause 19.1 did not give a star rating or any other specific criteria that would define 'deluxe', in Bayer Schering's view, the hotel's 5 star rating and membership of the LHW confirmed that it would inevitably be perceived as a 'deluxe' venue and thus its use for hospitality was not acceptable under the Code.

On 15 October, immediately after the meeting, Bayer Schering contacted Merck Serono with its concerns. Merck Serono confirmed that it had paid for UK delegates to stay at the hotel in question, but did not accept that its actions fell outside the Code. Merck Serono subsequently stated that an agent had inspected the hotel prior to the company confirming its booking.

Bayer Schering considered Merck Serono's responses inadequate because:

- *'There were only a few hotels that could accommodate us due to the usual massive demand for ECTRIMS 2007 hotel space and we selected this one as the most appropriate.'*

  Thus Merck Serono conceded that alternatives were available. However, even if lower quality hotels or no other hotels were available, there was nothing in the Code with regard to lack of availability of suitable alternatives being a defence for providing hospitality that would otherwise be considered inappropriate under Clause 19.1.

- *'Often Czech classified 5 or 4 star hotels would only register 3 or 4 stars in other parts of the world'*.

  Hotel quality, especially when comparing different countries, was highly subjective – one person's 'deluxe' might be another's 'adequate'. Accordingly, when selecting accommodation for sponsored health professionals, the impression given by the arrangements should be as important as the standards of the facilities. In Bayer Schering's view, a 5 star LHW would by definition be perceived as a lavish venue and the use of such a hotel for hospitality would not create a good impression of the industry. Additionally, membership of this luxury group would ensure consistent standards compared to other countries. LWH had confirmed that it had a consistent rating system throughout the world. Bayer Schering provided brief details of LWH's process for worldwide quality assurance.

- The hotel *'does not have a swimming pool nor fitness suite nor spa treatment facilities'*.

  However, as the hotel website noted, these were available nearby in a 'world class fitness centre club'; hotel guests could use all these facilities free of charge on presentation of a voucher. It was surprising that Merck Serono had not been told of this in the pre-booking inspection.

  Additionally, in Bayer Schering's opinion the presence or absence of fitness facilities and/or a pool on site was not necessarily relevant to the definition of deluxe. Many ordinary 3 and 4 star hotels had facilities such as pools and/or fitness equipment and many very exclusive deluxe hotels (especially in cities) did not.

When Bayer Schering told Merck Serono that it intended to complain formally to the Authority because it was not satisfied with Merck Serono's response, Merck Serono requested a face-to-face meeting to discuss a mutually agreeable and appropriate accommodation for our customers at next year's meetings … […] … in the spirit of the inter-company dialogue requested by the Code. However, Bayer Schering believed it had already engaged in considerable discussion over several weeks without receiving a satisfactory response, and that simply agreeing to avoid using inappropriately lavish accommodation in future could not undo any benefit Merck Serono might have gained from the hospitality already provided at ECTRIMS this year. Only a formal complaint upheld by the Authority would both reprimand Merck Serono publicly and clarify what constituted appropriate hospitality.

Bayer Schering would therefore be very grateful for the Authority's view on these events, and whether Merck Serono's hospitality arrangements at ECTRIMS were in breach of Clause 19.1. Should the Authority uphold Bayer Schering's complaint, in addition to reviewing its internal procedures for approval of hospitality arrangements, Bayer Schering believed it would be appropriate for Merck Serono to contact all UK health professionals who stayed at the hotel in order to inform them that the arrangements were in breach of the Code.

RESPONSE

Merck Serono stated that its UK delegates to the ECTRIMS meeting in Prague stayed in the hotel in question arranged for by an agency. Merck Serono discussed with the agency in advance of the meeting about the star rating and adherence to the Code (see below). The agency also visited the hotel.

Merck Serono had a rigorous system to ensure that all relevant materials were certified in line with the Code. It had acted in good faith in using this hotel and denied Bayer Schering's allegations. Merck Serono considered that rather than seeking clarification of Clause 19.1, as stated, Bayer Schering was demanding inappropriately punitive action for reasons that were unclear. Merck Serono tried to enter into constructive inter-company dialogue with Bayer Schering, which it declined after essentially one set of email exchanges and it decided to complain immediately to the Authority.

There were variations for hotel star rating classification across the world. The hotel used by Merck Serono was rated between 5 star and 3 star when viewing different systems and the hotel used by Bayer Schering was rated 4 star. Therefore the star rating system was fairly meaningless. The issue related more to whether the venue was lavish or deluxe, as stated in the Code, rather than the star rating. Furthermore the two hotels

were similar in standard but the hotel in question was near the congress centre (giving Merck Serono's customers easy access for the business reason that they were in Prague). The hotel used by Bayer Schering was 11 miles away, which might have been inconvenient for its customers.

Star rating

The star system and accommodation in Prague was not to the same standard as Western Europe. Often Czech classified 5 or 4 star hotels would only register 3 or 4 stars in other parts of the world.
The website of the hotel in question rated it as 5 star (as a member of the LHW group). LHW was a brand and marketing tool used by a profit-making organisation. It was not an independent quality standard. On two independent travel websites, the hotel was classified as 4 star (trip advisor) or 3 star (Frommer).

Merck Serono explained that there was a worldwide independent standard industry classification tool (hotel and travel index classification system) that most corporate travel companies used when assessing and booking hotels. The classification was Superior Deluxe, Deluxe, Moderate Deluxe, Superior First Class, First Class, Limited – Service First Class, Moderate First Class, Superior Tourist Class, Tourist Class and Moderate Tourist Class. The hotel was listed as Superior First Class.

The facilities, maintenance and general service in the Czech Republic were not to the same standard as Western European hotels. The hotel in question had two meetings rooms and business centre, restaurants, ground floor bar; it did not have an onsite swimming pool nor fitness suite or spa facilities. Bayer Schering stated that a nearby fitness centre was available to hotel guests. Leisure facilities were neither required nor sought by Merck Serono nor pointed out to its guests, nor were they obvious in the hotel. The invitation did not mention the hotel and so it could not have been an inducement to attend ECTRIMS with Merck Serono.

Lavish or deluxe?

At the same meeting, Bayer Schering accommodated its customers in a hotel which had an onsite fitness centre, offsite swimming pool and golf and first class amenities. It was situated in a centre with fantastic shopping and entertainment. The hotel website described luxury bedding etc. This was an example of the marketing terminology used to attract customers to the hotel and was not the same as that used in the Code and therefore not the same standard.

Merck Serono stated that its guests did not perceive the hotel it used to be deluxe or in any way plush; it was an adequate and appropriate small hotel to accommodate them for the purpose of the business and congress but nothing special. It did not exceed that level which the recipients would normally adopt when paying for themselves.

When the hotel used by Merck Serono (£115 B&B) and the hotel used by Bayer Schering (£96 B&B) were compared for price and facilities (no onsite leisure facilities vs onsite fitness) they were similar.

The hotel at issue was compliant with the Code, business appropriate, convenient to the congress centre (2 miles and close to metro) and a small hotel. Merck Serono believed that the issue for Bayer Schering might be that it booked a hotel (that was similar to its hotel in standard – see above) that was inconvenient for delegates (11 miles from the congress centre) and its customers had complained.

Additionally, when Merck Serono started looking for hotels, there were only a few that could accommodate it due to the usual high demand. Merck Serono considered a few hotels over the previous months; there was only one that met the requirements of the Code and could accommodate 58 people when Merck Serono booked. It was not unusual for hotels in cities to become heavily booked at times of international congresses.

In summary the Code stated:

1 'Lavish or deluxe venues must not be used; Merck Serono did not, feedback from attendees was that it was not deluxe accommodation.
2 The cost involved 'must not exceed that level which the recipients would normally adopt when paying for themselves' – Merck Serono did not.

Merck Serono therefore acted in good faith in agreeing to use this hotel.

Conclusion

Merck Serono denied that there had been 'considerable discussion over several weeks' as submitted by Bayer Schering and believed that Bayer Schering had acted precipitately and against the spirit of the inter-company dialogue requested by the Code. Although it stated that it wished to seek clarification of Clause 19.1, its request for further punitive action (review of internal procedures and writing to customers stating Merck Serono had breached the Code), and 'a formal complaint upheld by the PMCPA will both reprimand Merck Serono publicly' suggested it wanted more than that.

Merck Serono took adherence to the Code very seriously and it ensured that all its activities were appropriate and reasonable and that it maintained the ethical, professional and high standards expected from the Code.

PANEL RULING

The Panel noted that Clause 19.1 stated that the costs of hospitality must not exceed that level which recipients would normally adopt when paying for themselves. The supplementary information to Clause 19.1 stated that hospitality was limited to refreshments/subsistence (meals and drinks), accommodation, genuine registration fees and the

payment of reasonable travel costs which a company might provide to sponsor a delegate to attend a meeting. The supplementary information further stated that lavish and deluxe venues must not be used and that the impression that was created by the arrangements for any meeting must always be kept in mind. It should be the programme that attracted delegates and not the associated hospitality or venue. The Code did not prohibit the use of five star hotels per se. Some companies' own codes and policies prevented use of such hotels.

The Panel noted that Merck Serono's invitation to attend the ECTRIMS meeting in Prague had not referred to the hotel and so in that regard delegates could not have been attracted to the meeting by the accommodation being offered. It was convenient for the meeting venue and according to Merck Serono accommodation was limited. Nonetheless, accommodation had been provided at an hotel which was a member of the LHW group and more often than not rated five star and consistently described in terms of the luxury it provided, not only on its own website but also on others. Even allowing for differences in the star rating system, the impression was thus that Merck Serono's guests were being accommodated in a luxury hotel. The final breakdown of costs showed that one night's bed and breakfast accommodation cost £238 per person.

The Panel noted that almost half of Merck Serono's sponsored delegates were nurses. In the Panel's view the cost of accommodation was more than most people might be expected to pay if they were paying for themselves; it was higher than nurses would normally pay.

On balance, the Panel considered that excessive hospitality had been provided. A breach of Clause 19.1 was ruled.

Complaint received	**21 November 2007**
Case completed	**7 January 2008**

ANONYMOUS COMPLAINANTS v BRISTOL-MYERS SQUIBB and OTSUKA

Alleged inappropriate hospitality

Two separate complaints were made by anonymous groups of complainants about Bristol-Myers Squibb and Otsuka providing inappropriate hospitality to a group of psychiatrists, the South Asian Psychiatric Forum. The two companies promoted Abilify (aripiprazole).

In Case AUTH/2070/11/07, the complainants stated that Otsuka had sponsored a weekend conference for the South Asian Psychiatric Forum, the members of which enjoyed hospitality at the expense of the company. Some psychiatrists were able to stay with their wives at the hotel in Birmingham, where the meeting was held.

This group of psychiatrists invited speakers and friends to attend. It was like a nexus. They had numbers and the company needed to boost its sales.

The complainants requested a formal investigation: as to whether the company had breached the Code; were the speakers' lectures approved by the ABPI; who invited and selected the speakers; why the company sponsored the event; and what was the nexus between the company and the organisers of the South Asian Forum?

In Cases AUTH/2072/12/07 and AUTH/2073/12/07, the complainants complained about Bristol-Myers Squibb and Otsuka's promotion of Abilify.

Otsuka sponsored a meeting for the South Asian Forum. Fifty hotel rooms were booked for the group. It was not a scientific conference. The Forum invited its own speakers and all the money for entertainment was paid by the company.

It would be worth investigating: whether there was a nexus between these companies and the organisers of the South Asian Forum and whether there was a breach of the Code with regard to inappropriate hospitality.

The Panel noted that the meeting, 'Recent Advances in Management of Schizophrenia', had been jointly sponsored by Otsuka and Bristol-Myers Squibb. The agendas provided by the complainants and companies differed. Each bore an identical company reference number but that provided by the complainants did not include a declaration of sponsorship and there were minor differences in the speaker details, etc. The Panel noted the companies' submission in this regard. The complainants were anonymous and non-contactable. The agenda supplied by the companies showed that there were one and a half hours of education on the Friday evening followed by dinner. On Saturday the educational programme ran from 09.15 to 15.45 with an hour for lunch. The Panel considered that, according to the agenda, the scientific/educational content was not unreasonable for sponsorship by a pharmaceutical company. The prime purpose of the meeting was educational.

The Panel noted that sponsorship of the meeting had included provision of speakers' honoraria, the hire of meeting rooms and equipment, meals and beverages and overnight accommodation as required. Thirty nine of the 69 delegates stayed overnight on the Friday. No entertainment had been provided for those staying overnight. The Panel considered that the costs involved in the meeting were modest and did not exceed that level which recipients would normally adopt when paying for themselves. The Panel noted that only spouses who qualified as delegates to the meeting in their own right had been invited. This had involved five couples. The companies had taken steps to ensure that uninvited partners did not attend the meeting.

On the basis of the information before it, the Panel did not consider that there had been a breach of the Code.

Two separate complaints were made by anonymous groups of complainants about Bristol-Myers Squibb Pharmaceuticals Ltd and Otsuka Pharmaceuticals (UK) Ltd providing inappropriate hospitality at a meeting. The two companies worked together for the co-development and promotion of Abilify (aripiprazole).

Case AUTH/2070/11/07

COMPLAINT

The complainants stated that Otsuka had sponsored a weekend conference in November 2007 for a group of psychiatrists, the South Asian Psychiatric Forum, which enjoyed hospitality at the expense of the company. Some psychiatrists were able to stay with their wives at the hotel in Birmingham, where the meeting was held.

These psychiatrists invited their speakers and friends to attend the event and Otsuka agreed to sponsor. It was like a nexus. They had numbers and the company needed to boost its sales.

There should be a formal investigation:

1) as to whether the company had breached the Code;
2) were the speakers' lectures approved by the ABPI;
3) who invited and selected the speakers;
4) why the company sponsored the event;
5) what was the nexus between the company and the organisers of the South Asian Forum?

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

Cases AUTH/2072/12/07 and AUTH/2073/12/07

COMPLAINT

The complainants complained about Bristol-Myers Squibb and Otsuka's promotion of Abilify, an Otsuka antipsychotic product.

Otsuka sponsored a meeting for the South Asian Forum which was an association. Fifty hotel rooms were booked for the group. It was not a scientific conference. The organisers of the Forum invited their own speakers and all the money for entertainment was paid by the company.

It would be worth investigating:

1) whether there was a nexus between these companies and the organisers of the
South Asian Forum;
2) whether there was a breach of the Code with regard to inappropriate hospitality.

When writing to the Otsuka and Bristol-Myers Squibb the Authority asked them to respond in relation to Clauses 2, 9.1 and 19.1.

Cases AUTH/2070/11/07, AUTH/2072/12/07 and AUTH/2073/12/07

RESPONSE

Bristol-Myers Squibb and Otsuka submitted a joint response. The companies believed the allegations were untrue. Both companies had taken all necessary steps to ensure that they had adhered to the Code as was their practice at all times. The companies did not believe that they had breached Clauses 2, 9.1 and 19.1.

The companies agreed with the South Asian Forum to be sole sponsors of its scientific meeting in November 2007. The sponsorship included provision of speakers' honoraria, the hire of meeting rooms and equipment, meals and beverages and overnight accommodation as required. The meeting consisted of 6 hours 30 minutes of scientific content; 1 hour 30 minutes on Friday evening and 5 hours on the Saturday. The meeting was open to health professionals with an interest in psychiatry and members of the South Asian Forum. Appropriate health professionals were invited by the South Asian Forum from all over the UK and by company representatives. Delegates were invited to attend the scientific meeting on both Friday and Saturday. Sixty-nine health professionals attended together with 5 speakers and a chairperson.

Sponsorship of the meeting was clearly identified on the front of the approved invitation by Bristol-Myers Squibb and Otsuka. Although the meeting was primarily educational in nature, because both companies had one product, Abilify, licensed for schizophrenia and there was a reference to that disease in the agenda, the companies included the prescribing information.

A draft invitation and agenda were created by Bristol-Myers Squibb and Otsuka in collaboration with the chairperson for planning purposes only. The companies noted from the version the Authority sent them that this was different to the final approved version. The final approved version was provided. The companies were unsure of the origin of the version provided by the complainants to the Authority and had been unable to contact the chairperson to obtain his assistance in this regard.

Bristol-Myers Squibb and Otsuka in collaboration with the chairperson helped source suitable academic speakers. The scientific programme included a number of eminent speakers who were paid honoraria for preparing and delivering their lectures. This was paid by Bristol-Myers Squibb and Otsuka as per company standard operating procedures (SOPs) and speaker agreements.

The level of hospitality provided was appropriate for such a scientific meeting.

The venue was selected based on its appropriateness, excellent conference facilities and central location. An agency sourced the venue.

For delegates, meals and beverages were provided for Friday evening after the academic session which were modest in terms of costs (£36.81 per head) and quantity. The overall cost per head for the two day meeting was £134.20. The total cost for the 2 day meeting was £9,259.58. Lunch and coffee breaks were provided on the Saturday as part of a day delegate rate (£60 per person). Details of the quantities and types of meal and beverage were provided.

As this was planned as a two day meeting and many delegates were coming from across the UK, accommodation was provided as an option. Not all delegates took up this option. Of 69 delegates, accommodation was provided for only 39. No entertainment was provided at any time during the meeting.

No-one was invited simply as a partner of a delegate. The invitation was provided to health professionals only. There were delegates who, as health professionals in their own right, also happened to be partners of other delegates, a situation which was clearly in accordance with the supplementary information to Clause 19.1, which permitted provision of hospitality to a spouse who was a member of the health professions, and qualified as a proper delegate at the

meeting in their own right. This involved five couples.

The companies gave clear verbal instructions to the hotel that uninvited partners were not acceptable and asked the hotel to advise them of any delegate who tried to check-in a partner who was not an invited delegate. In addition, the companies advised the hotel that all rooms being paid for would be for single occupancy.

In summary, the companies believed they complied fully with the Code and that the allegations were unfounded. Bristol-Myers Squibb and Otsuka therefore denied a breach of Clauses 2, 9.1 or 19.1.

PANEL RULING

The Panel noted that the meeting, 'Recent Advances in Management of Schizophrenia', had been jointly sponsored by Otsuka and Bristol-Myers Squibb. The agendas provided by the complainants and companies differed. Each bore an identical company reference number but that provided by the complainants did not include a declaration of sponsorship and there were minor differences in the speaker details, etc. The Panel noted the companies' submission in this regard. The complainants were anonymous and non-contactable. The agenda supplied by the companies showed that there were one and a half hours of education on the Friday evening followed by dinner. On Saturday the educational programme ran from 09.15 to 15.45 with an hour for lunch. The Panel considered that, according to the agenda, the scientific/educational content was not unreasonable for sponsorship by a pharmaceutical company. The prime purpose of the meeting was educational.

The Panel noted that sponsorship of the meeting had included provision of speakers' honoraria, the hire of meeting rooms and equipment, meals and beverages and overnight accommodation as required. Thirty-nine of the 69 delegates stayed overnight on the Friday. No entertainment was provided at any time during the meeting. The Panel considered that the costs involved in the meeting were modest and did not exceed that level which recipients would normally adopt when paying for themselves. The Panel noted that only spouses who qualified as delegates to the meeting in their own right had been invited. This had involved five couples. The companies had taken steps to ensure that uninvited partners did not attend the meeting.

On the basis of the information before it, the Panel did not consider that there had been breaches of Clauses 2, 9.1 and 19.1 and ruled accordingly.

Complaints received
Case AUTH/2070/11/07 28 November 2007
Case AUTH/2072/12/07 3 December 2007
Case AUTH/2073/12/07 3 December 2007

Cases completed 7 January 2008

CASE AUTH/2074/12/07

GP PRACTICE MANAGER v ASTRAZENECA

Conduct of a representative

A GP practice manager complained about the conduct of a representative of AstraZeneca. The representative accompanied his young child who was registered as a patient at the practice for a booked appointment. Towards the end of the consultation the representative produced Symbicort sales literature which he placed on the doctor's desk. The doctor considered that it was inappropriate to use private consultation time to solicit sales information.

The Panel noted that the representative, at the end of an appointment for his young child, had left some sales material with the GP. AstraZeneca had submitted that this was to fulfil a request of another doctor in the practice that material be left next time the representative was passing. As acknowledged by AstraZeneca, such behaviour was misguided and showed poor judgement. The Panel considered that by providing sales material during a professional, medical appointment with a doctor, the representative had not maintained a high standard of ethical conduct. Breaches of the Code were ruled. The Panel considered that although the representative's behaviour was unacceptable, it was not such as to warrant a ruling of a breach of Clause 2.

A GP practice manager complained about the conduct of a representative of AstraZeneca UK Limited.

COMPLAINT

The complainant explained that the representative, who was also registered as a patient at the practice, attended a doctor's appointment with his young child for whom an appointment had been booked. Towards the end of the consultation the representative produced sales literature which he placed on the doctor's desk, detailing 'Symbicort Smart'. The doctor considered that this was a completely inappropriate use of private consultation time, to solicit sales information.

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

RESPONSE

AstraZeneca submitted that the representative attended an appointment for his child at his GP surgery and after the consultation, on leaving, he handed the GP a promotional item. He did this proactively. He was misguided in believing this action fulfilled a request made by another GP in the surgery on a previous occasion that he should simply leave this material with the practice the next time he was passing. The spirit of the Code suggested that had the representative made an appointment for his child specifically to gain an interview with the GP, this would indeed be a breach of Clause 15.2. This was not the case. The representative believed this was in accordance with a request made by another GP at the same practice. Although poor judgement and misguided belief led this representative to this opportunistic error, AstraZeneca accepted it was in breach of Clause 15.2.

AstraZeneca explained that it took very seriously all allegations of inappropriate conduct and representatives were trained on the Code and took the ABPI examination. In addition, training on Code awareness was cascaded through sales managers to individual representatives every quarter, in order to understand recent case rulings and share learning. In spite of all this, if an individual deliberately breached the Code and company policies, there was little that could be done.

As with case precedent, sometimes there were unusual situations that could not be known beforehand, accounted for and trained out until unfortunately they occurred. Whilst this meant that they could not be prevented from occurring, it also meant further action would be taken.

In this case, the representative had read the policies (including the Code) and had had his knowledge validated. This and a number of field visits provided sufficient reassurance for his managers to feel he was doing a good job. However there were consequences should anyone choose not to adhere to what was clearly set out in these policies and this was taken very seriously by AstraZeneca. Investigations into the performance and conduct of the representative had already started, according to AstraZeneca's disciplinary process.

AstraZeneca had mandatory training, validation and several policies in respect to Code compliance for all employees. No one could claim they were unaware of these obligations. It therefore followed that this individual had breached recognised company standards, rather than the company had breached Code standards. However, the company was accountable for the conduct of its employees.

AstraZeneca hoped that it had demonstrated that its standards were high and did not bring the industry into disrepute. The company therefore did not believe that there had been a breach of Clauses 9.1 or 2.

In conclusion, AstraZeneca stated that from its internal investigation it was disappointed to learn that the

representative had deliberately acted against the letter and spirit of AstraZeneca policies and the Code. His failure to apply good judgement and common sense had warranted further investigation. AstraZeneca sincerely apologised to the GP concerned.

PANEL RULING

The Panel noted that the representative had taken the opportunity, at the end of an appointment for his young child, to leave some sales material with the GP. AstraZeneca had submitted that this was to fulfil a request of another doctor in the practice that material be left next time the representative was passing. As acknowledged by AstraZeneca, such behaviour was misguided and showed poor judgement. The Panel considered that by providing sales material during a professional, medical appointment with a doctor, the representative had not maintained a high standard of ethical conduct. Breaches of Clauses 9.1 and 15.2 were ruled.

The Panel considered that although the representative's behaviour was unacceptable, it was not such as to warrant a ruling of a breach of Clause 2 of the Code which was a sign of particular censure and reserved for such use. No breach of Clause 2 was ruled.

Complaint received 7 December 2007

Case completed 22 January 2008

GENERAL PRACTITIONER v MERCK SHARP & DOHME

Packaging for a promotional aid

A general practitioner complained that although Arcoxia was printed on the packaging of an Arcoxia (etoricoxib) promotional aid (a USB flash drive) issued by Merck Sharp & Dohme, there was no mention of the approved name (etoricoxib).

The Panel considered that the USB flash drive, together with its packaging, comprised the promotional aid. With regard to the name of a medicine, the Code required that as long as promotional aids included no more than the brand name or the non-proprietary name, then prescribing information need not be included. It was, thus, acceptable on promotional aids to only include the brand name; to also include the non-proprietary name would trigger the requirement to include prescribing information. The Panel considered that the promotional aid met the requirements of the Code and no breach was ruled.

A general practitioner complained about the packaging of an Arcoxia (etoricoxib) promotional aid issued by Merck Sharp & Dohme Limited.

COMPLAINT

The complainant explained that he had recently responded to an invitation to request a USB flash drive from Merck Sharp & Dohme. The complainant noted that the packaging in which the gift arrived had Arcoxia printed on it in four places, however, there was no mention of the approved name (etoricoxib). The complainant considered that the packaging was clearly promotional and as such the most prominent occurrence of the name should be accompanied by the approved name.

When writing to Merck Sharp & Dohme, the Authority asked it to respond in relation to Clauses 4.3, 9.1 and 18.3 of the Code.

RESPONSE

Merck Sharp & Dohme submitted that in its view the item in question complied with the requirements for promotional aids, defined in the Code.

The company stated that it considered the promotional aid to be the USB flash drive together with its box. Merck Sharp & Dohme noted that the box had a window through which the USB key itself was clearly visible. The company believed therefore that the packaging was an integral part of the promotional aid, and was therefore subject to Clause 18.3. The box was intended to be disposed of once the USB stick was removed. Indeed, the complainant described the material as the packaging that the promotional aid was delivered in.

Clause 18.3 applied to the complete promotional aid, which as noted above comprised the USB key and its packaging. Clause 18.3 prohibited it from including both brand and non-proprietary names. Thus it disagreed with the complainant's assertion that the approved name should have been included.

Merck Sharp & Dohme believed that it always applied high standards through the application of its medico-legal approval process and denied a breach of Clause 9.1.

The company did not believe Clause 4.3 applied in this instance as Clause 18.3 specifically stated that the prescribing information required under Clause 4 did not have to be included on a promotional aid if the promotional aid included, *inter alia*, no more than the brand name of the medicine. Merck Sharp & Dohme did not accept that the box in question could reasonably be construed as anything other than the packaging of a promotional aid, and was intended to be disposed of once the memory stick had been removed.

In summary, Merck Sharp & Dohme did not believe that its actions had breached Clauses 4.3, 9.1 and/or 18.3 of the Code.

PANEL RULING

The Panel considered that the USB flash drive, together with its packaging, comprised the promotional aid. Clause 18.3 of the Code stated, with regard to the name of a medicine, that as long as promotional aids included no more than the brand name or the non-proprietary name, then prescribing information about the medicine need not be included. It was, thus, acceptable on promotional aids to only include the brand name; to also include the non-proprietary name would trigger the requirement to include prescribing information under Clause 4.1. The Panel considered that the promotional aid met the requirements of Clause 18.3 and no breach of that clause was ruled. There was no need to include prescribing information and so no breach of Clause 4.1 was ruled. The Panel considered that high standards had been maintained. No breach of Clause 9.1 was ruled.

Complaint received	**11 December 2007**
Case completed	**25 January 2008**

CASE AUTH/2076/12/07

HOSPITAL PHARMACIST v ABBOTT

Conduct of a representative

A hospital pharmacist, complained that a representative of Abbott Laboratories had paged her and, *inter alia*, asked her if she could increase the order for Kaletra in December. When the complainant asked why, the representative stated that it was so that he could get his Christmas bonus. The complainant considered that this was inappropriate behaviour. The complainant further submitted that paging should be for urgent enquiries, not for the issues referred to by the representative.

The Panel noted Abbott's submission that the representative and the complainant had known one another for seven years. In the Panel's view it was likely that a degree of informality might exist in meetings between the two. Nonetheless such meetings must comply with the Code. Representatives should always conduct their business in an ethical manner and so to ask, even in jest, for a hospital to increase its order for a product as a means of getting a Christmas bonus, was unacceptable. The Panel considered that high standards had not been maintained. A breach of the Code was ruled as acknowledged by Abbott.

The Panel noted the parties' submissions regarding the acceptability of paging and length of the relationship. The Panel considered that, on the balance of probability, it was the established custom and practice for the representative to page the complainant. In that regard the Panel considered that the representative had the complainant's permission to page her. No breach of the Code was ruled in that regard.

A lead hospital pharmacist, HIV/ID and antimicrobials, complained about the conduct of a representative from Abbott Laboratories Ltd

COMPLAINT

The complainant stated that the representative had paged her and, *inter alia*, asked her if she could increase the order for Kaletra in December. When the complainant asked why, the representative admitted that it was so that he could get his Christmas bonus. The complainant considered that this was inappropriate behaviour.

In an email to the Authority, giving permission for her identity to be revealed to Abbott, the complainant had spoken to her manager about the complaint who had suggested that it was noted that the representative had paged the complainant whilst she was in a meeting and never even asked if it was okay to speak. The complainant submitted that paging should be for urgent enquiries, not for the issues referred to by the representative.

When writing to Abbott, the Authority asked it to respond in relation to Clauses 9.9 and 15.2 of the Code.

RESPONSE

Abbott confirmed that the representative had paged the complainant without her prior permission. The representative had known the complainant for seven years, in which time this method of communication had been accepted practice and he therefore assumed that it would be so on this occasion.

The representative accepted that in not gaining explicit permission to page the complainant to discuss an Abbott product he was in breach of the Code. He further acknowledged that he had not received any instructions or direction from his manager to pursue this line of enquiry regarding placement of orders and in doing so had acted against Abbott's Code of Business Conduct. The representative was extremely apologetic that he had upset the complainant.

Abbott thus accepted that the representative had acted in breach of both Clauses 9.9 and 15.2 of the Code. His actions had also contravened Abbott's Code of Business Conduct and formal disciplinary action would be taken in accordance with the company's procedures.

FURTHER COMMENTS FROM THE COMPLAINANT

In response to a question from the Authority with regard to whether paging was an accepted method of communication between the complainant and the representative, the complainant stated that the issue was not specifically that the representative had paged her at a meeting – although representatives did not generally page consultants. The complainant stated that the issue was that the representative had asked her to increase the order of Kaletra so that he could get his Christmas bonus. With regard to paging, the complainant submitted that she and the representative had never discussed appropriate ways of contacting her.

PANEL MINUTE

The Panel noted Abbott's submission that the representative and the complainant had known one another for seven years. In the Panel's view it was likely that a degree of informality might exist in meetings between the two. Nonetheless such meetings must comply with the Code. Representatives should always conduct their business in an ethical manner and so to ask, even in jest, for a hospital to increase its order for a product as a means of getting a Christmas bonus, was unacceptable. The Panel considered that high standards had not been maintained. A breach of

the Clause 15.2 was ruled as acknowledged by Abbott.

The Panel noted the parties' submissions regarding the acceptability of paging and length of the relationship. The Panel considered that, on the balance of probability, it was the established custom and practice for the representative to page the complainant. In that regard the Panel considered that the representative had the complainant's permission to page her. No breach of Clause 9.9 was ruled.

Complaint received 25 November 2007

Case completed 31 January 2008

CASE AUTH/2077/1/08

GENERAL PRACTITIONER v PFIZER

Invitation to receive an Arthrotec memory stick

A general practitioner complained that a reply paid card from Pfizer offering an Arthrotec (diclofenac/misoprostol) memory stick did not include the approved name despite the promotional heading 'Remember Arthrotec'.

The Panel noted that the mailing in question consisted of a leaflet detailing Arthrotec and a wholly separate reply paid card. The reply paid card had Pfizer's address on one side and the other was headed 'Remember Arthrotec'. There was no reference at all to the non-proprietary name on the reply paid card.

The Panel considered that the reply paid card was a promotional item in its own right; it was not, for instance, provided as a tear-off section of the main leaflet ie physically part of the leaflet. It thus had to stand alone with respect to the requirements of the Code. The card bore the name of the product, Arthrotec and was not exempt from the requirement to provide prescribing information. One of the components of prescribing information was the non-proprietary name of the product. As there was no mention at all of the non-proprietary name on the reply paid card, the Panel ruled a breach of the Code.

The Panel noted that if the reply paid card had been provided as a physical part of the main leaflet then it would not have been a stand alone piece and could have relied on the prescribing information being printed on the larger leaflet. The Panel further noted that although its ruling suggested that prescribing information was required, in this instance it could have been included because the card in question was such that for posting, it was folded in half and stuck down so that all that was visible on the outside, and therefore to the public, was the address.

A general practitioner complained about a reply paid card (ref ART-035-07) from Pfizer Limited offering him an Arthrotec (diclofenac/misoprostol) memory stick. The reply paid card was part of a GP mailing which consisted of a promotional leaflet together with the reply paid card in an envelope.

COMPLAINT

The complainant stated that this was an invitation to receive a complimentary memory stick and since the heading on the top was 'Remember Arthrotec' it clearly served a promotional purpose. However, the approved name did not appear anywhere in the document.

When writing to Pfizer, the Authority asked it to respond in relation to Clause 4.1 of the Code.

RESPONSE

Pfizer noted that the supplementary information to Clause 4.1 stated 'Each promotional item for a medicine must be able to stand alone'. The item in question was a reply paid card which Pfizer did not deem to be promotional as it did not make any claims, and which therefore not need to include any prescribing information as required under Clause 4.1.

The supplementary information on reply paid cards in Clause 9.8 stated 'Reply paid cards which are intended to be returned to companies through the post and which relate to a prescription only medicine should not bear both the name of the medicine and information as to its usage but may bear one or the other'. In line with this guidance the reply paid card stated the brand name of the medicine and did not bear any information as to its usage, therefore ensuring there was no breach of Clause 9.8.

In conclusion, Pfizer did not believe any of the items within the mailing to be in breach of the Code.

PANEL RULING

The Panel noted that the mailing in question consisted of a leaflet detailing Arthrotec and a wholly separate reply paid card. Both items had the same reference number (ART-035-07). The reply paid card had Pfizer's address on one side and the other was headed 'Remember Arthrotec'. There was no reference at all to the non-proprietary name on the reply paid card.

The Panel considered that the reply paid card was a promotional item in its own right; it was not, for instance, provided as a tear-off section of the main leaflet ie physically part of the leaflet. It thus had to stand alone with respect to the requirements of the Code. The card bore the name of the product, Arthrotec. The Panel noted that Clause 4.1 required the prescribing information listed in Clause 4.2 to be provided in a clear and legible manner in all promotional material for a medicine except for abbreviated advertisements and promotional aids. The reply paid card was neither an abbreviated advertisement nor a promotional aid and so was not exempt from the requirement for prescribing information to be provided. One of the components of prescribing information as listed in Clause 4.2 was the non-proprietary name of the product. As there was no mention at all of the non-proprietary name on the reply paid card, the Panel ruled a breach of Clause 4.1.

The Panel noted that Pfizer had referred to Clause 9.8 implying that meeting the requirements of that clause was incompatible with also complying with Clause 4.1.

This was not so. If the reply paid card had been provided as a physical part of the main leaflet then it would not have been a stand alone piece and could have relied on the prescribing information being printed on the larger leaflet. The company would then have only had to comply with Clause 9.8 of the Code ie that reply paid cards returned through the post to companies should not bear both the name of the medicine and information as to its use. The Panel noted that although its ruling above suggested that prescribing information was required, in this instance it could have been included on the reply paid card in question without, at the same time, breaching Clause 9.8 because the card was such that when the doctor sent it back through the post it was folded in half and stuck down so that all that was visible on the outside, and therefore to the public, was the address.

Complaint received	**7 January 2008**
Case completed	**31 January 2008**

CODE OF PRACTICE REVIEW – FEBRUARY 2008

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

2007/5/07	**Trinity-Chiesi v Teva**	**Qvar leavepiece**	**Breach Clause 7.2**	**Appeal by respondent**	**Page 3**
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2038/8/07	**Novo Nordisk v Sanofi-Aventis**	**Promotion of Lantus**	**Breach Clause 3.2, Two breaches Clause 7.2 Breach Clause 7.4**	**Appeal by respondent**	**Page 80**
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2055/10/07	**Voluntary admission by UCB Pharma**	**Promotion of prescription only medicine to the public**	**Breaches Clauses 2, 9.1, 20.1 and 20.2**	**No appeal**	**Page 117**
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2059/10/07	**Primary Care Trust Medicines Management Director v Janssen-Cilag**	**Risperdal Consta journal advertisement**	**Breaches Clauses 3.2, 7.2 and 7.8**	**No appeal**	**Page 138**

2061/10/07 and 2062/10/07	**Wyeth v Lilly and Boehringer Ingelheim**	**Cymbalta detail aid**	**Breaches Clauses 7.2, 7.3, 7.4 and 7.8**	**No appeal**	**Page 140**
2063/10/07	**Consultant Physician v Abbott**	**Invitation to an advisory board**	**Breach Clause 9.1**	**Appeal by respondent**	**Page 144**
2064/11/07	General Practitioner v Roche	Conduct of a representative	No breach	No appeal	Page 148
2067/11/07	**Johnson & Johnson Consumer Services Eame v Pfizer**	**Smoking cessation campaign**	**Breach Clause 20.2**	**No appeal**	**Page 150**
2068/11/07	**Bayer Schering Pharma v Merck Serono**	**Hospitality at international meeting**	**Breach Clause 19.1**	**No appeal**	**Page 154**
2070/11/07, 2072/12/07 and 2073/12/07	Anonymous complainants v Bristol-Myers Squibb and Otsuka	Alleged inappropriate hospitality	No breach	No appeal	Page 158
2074/12/07	**GP practice manager v AstraZeneca**	**Conduct of a representative**	**Breaches Clauses 9.1 and 15.2**	**No appeal**	**Page 161**
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2076/12/07	**Hospital Pharmacist v Abbott**	**Conduct of a representative**	**Breach Clause 15.2**	**No appeal**	**Page 164**
2077/1/08	**General Practitioner v Pfizer**	**Invitation to receive an Arthrotec memory stick**	**Breach Clause 4.1**	**No appeal**	**Page 166**

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.