PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

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

Annual Report for 2004

The Annual Report of the Prescription Medicines Code of Practice Authority for 2004 has now been published and copies have been sent to all who are on the mailing list for the Code of Practice Review. Further copies are available on request.

As previously reported in the Review, there were 119 complaints in 2004 as compared with 131 in 2003. There were 127 complaints in 2002.

The 119 complaints in 2004 gave rise to 119 cases, which was less than in 2003. Ordinarily the number of cases differs from the number of complaints, the reason being that some complaints involve more than one respondent company and some complaints do not become cases at all, usually because no *prima facie* case is established.

Of the 424 rulings made by the Code of Practice Panel in 2004, 357 (84.2%) were accepted by the parties, 48 (11.3%) were unsuccessfully appealed and 19 (4.5%) were successfully appealed. This compares with the 5.5% of rulings which were successfully appealed in 2003.

The Code of Practice Panel met 86 times in 2004 (88 in 2003) and the Code of Practice Appeal Board met 10 times in 2004 (13 in 2003). The Appeal Board considered appeals in 23 cases as compared with 29 in 2003.

The number of complaints made by health professionals in 2004 exceeded the number made by pharmaceutical companies, there being 48 from health professionals and 46 from pharmaceutical companies. This has historically been the usual pattern but it has not been the case in four out of the last six years. Complaints made by pharmaceutical companies are usually more complex than those from outside the industry and generally raise a number of issues.

Advice on advisory boards

It is acceptable for companies to arrange advisory board meetings and the like and to pay health professionals and others for advice on subjects relevant to their products. Nonetheless, the arrangements for such meetings have to comply with the Code. As with promotional meetings the requirements as to hospitality being of a reasonable standard etc, as set out in Clause 19 of the Code, have to be followed. The choice and number of delegates should stand up to independent scrutiny. Each should be chosen according to their expertise such that they will 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 number of meetings and the number of delegates at each should be driven by need and not the invitees' willingness to attend. Invitations to participate in an advisory board meeting should state the purpose of the meeting and the expected advisory role and amount of work to be undertaken. If an honorarium is offered it should be clear that it is a payment for such work and advice. Honoraria must be commensurate with the time and effort involved and the professional status of the recipients.

Target your mailings

Companies are reminded that it is a requirement of the Code that promotional material should be sent only to those people whose need for, or interest in, the particular information can reasonably be assumed. Material for clinicians might not be appropriate for use with administrative staff. Similarly material sent to one medical speciality might not be appropriate for another. Clause 12.1 refers. Companies must ensure that mailings are properly targeted so that they comply with the Code in this regard. Mailings sent to a diverse audience but written on the basis of 'one size fits all' are likely to be unacceptable.

Dr Susan Bews

Dr Susan Bews, Medical Director, Astellas Pharma Ltd, has retired from the Code of Practice Appeal Board and from Astellas. Dr Bews joined the then Code of Practice Committee in 1987 and was the longest serving member. At her last meeting of the Appeal Board the Chairman noted that Dr Bews had made an outstanding contribution to its work. We wish her a very long and happy retirement.

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 date on which places remain available is:

Monday, 5 December

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

For further information regarding any of the above, please contact Jean Rollingson for details (020 7930 9677 extn 4).

How to contact the Authority

Our address is:

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www.pmcpa.org.uk

Telephone: 020 7930 9677
Facsimile: 020 7930 4554

Copies of the Code of Practice for the Pharmaceutical Industry and of this Review can be obtained from Lisa Matthews (020 7930 9677 extn 5).

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

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

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

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

CASE AUTH/1622/8/04

AVENTIS PHARMA v NOVO NORDISK

Levemir mailing

Aventis Pharma complained about a mailing for Levemir (insulin detemir) issued by Novo Nordisk. Aventis supplied Lantus (insulin glargine).

The heading 'Levemir FlexPen – a new basal insulin analogue for people with diabetes who need' was followed by the claims 'a more predictable profile than glargine and NPH [neutral protamine hagedom]'; 'fewer nocturnal hypoglycaemic events than NPH'; 'more effective glycaemic control than NPH' and 'no undesirable weight gain'. Aventis stated that, taken overall, the heading suggested that Levemir FlexPen was an appropriate treatment for all individuals with diabetes who had the four requirements listed in the claims.

In order to substantiate each of the four claims, Novo Nordisk must be able to provide data for Levemir in patients with both type 1 and type 2 diabetes. Aventis noted that the cited references only referred to studies conducted in patients with type 1 diabetes. Novo Nordisk had not provided evidence to substantiate these claims for Levemir in all people with diabetes. Aventis therefore alleged that the four claims were inaccurate, unsubstantiated and exaggerated.

With regard to the claim 'a more predictable profile than glargine and NPH' the Panel noted that Section 5.1 of the Levemir summary of product characteristics (SPC) stated that the time action profile of insulin detemir was statistically significantly less variable than for NPH insulin. There was no comparable statement for insulin glargine. Novo Nordisk submitted a number of studies to support the statement in the SPC with regard to NPH both in type 1 and type 2 diabetics. Two papers reporting one study (Heise *et al*) were submitted comparing, *inter alia*, insulin detemir (n=18) and insulin glargine (n=16) in type 1 diabetics. In the Panel's view, however, the size of the study was too small to be used as the sole basis for a comparable efficacy claim vs insulin glargine in type 1 diabetics. No data in type 2 diabetics had been provided. The Panel considered that it had not been established that Levemir had a more predicable profile than glargine and in that regard the claim 'a more predictable profile than glargine and NPH' was inaccurate, unsubstantiated and exaggerated as alleged. The Panel ruled breaches of the Code.

Upon appeal by Novo Nordisk the Appeal Board noted that Heise *et al*, rejected by the Panel as being too small was, in terms of a clamp study, the largest known and in that regard substantiated the claim at issue with regard to insulin glargine and type 1 diabetics. The pharmacodynamic profile of exogenous insulin was more readily demonstrated in type 1 diabetics and in that regard the Appeal Board further considered that the study was a validated methodology broadly applicable to both type 1 and type 2 diabetics. The Appeal Board noted the outcome of the clamp study and the statement in the Levemir SPC and considered that the claim at issue was capable of substantiation and not inaccurate or exaggerated as alleged. The Appeal Board ruled no breaches of the Code.

With regard to the claim 'fewer nocturnal hypoglycaemic events than NPH' the Panel noted that Section 5.1 of the Levemir SPC stated, with regard to type 1 diabetes, that there was a lower risk of nocturnal hypoglycaemia with Levemir than with NPH insulin. It was further stated that analyses of nocturnal hypoglycaemia in type 1 diabetes showed a significantly lower risk of minor nocturnal hypoglycaemia than with NPH insulin, whereas no difference was seen with type 2 diabetes.

Two papers were submitted by Novo Nordisk which dealt solely with the treatment of type 2 diabetics; one reported that the risk of nocturnal hypoglycaemia was reduced by 55% in patients treated with insulin detemir compared with NPH-treated patients ($p<0.001$) but the other reported that a 38% decrease in the risk observed in patients treated with insulin detemir compared with NPH-treated patients was not statistically significant. On balance the Panel thus considered that there was insufficient data to claim that all diabetics treated with insulin detemir would have fewer nocturnal hypoglycaemic events than if they had been treated with NPH. There was the data to show that this was the case in type 1 diabetics but insufficient data in type 2. The Panel noted the SPC statement in this regard. The Panel thus considered that the claim was inaccurate, misleading and exaggerated as alleged. Breaches of the Code were ruled which were upheld on appeal by Novo Nordisk.

With regard to the claim 'more effective glycaemic control than NPH' the Panel noted that Section 5.1 of the Levemir SPC stated 'In long-term treatment trials, fasting plasma glucose in patients with type 1 diabetes was improved with Levemir compared with NPH insulin when given as basal/bolus therapy. Glycaemic control (HbA_{1c}) with Levemir is comparable to NPH insulin, with a lower risk of nocturnal hypoglycaemia and no associated weight gain'. The Panel thus considered that, in the context in which it appeared in the SPC, the statement about glycaemic control related only to type 1 diabetics.

The Panel considered that the majority of readers would assume that 'glycaemic control' referred to the measurement of HbA_{1c} as implied in the Levemir SPC. The SPC stated that, in type 1 diabetics, glycaemic control with Levemir was comparable to NPH insulin and the majority of the papers submitted by Novo Nordisk supported this statement. Only two studies reported statistically significant advantages for insulin detemir compared with NPH insulin. The balance of evidence was thus that the two insulins were comparable in type 1 diabetics.

With regard to type 2 diabetics only two studies had compared insulin detemir and NPH insulin in this group. Both groups reported that, in terms of HbA_{1c}, the two insulins were comparable.

The Panel thus considered that, the claim 'More effective glycaemic control than NPH' was inaccurate, misleading and exaggerated as alleged. Breaches of the Code were ruled which were upheld on appeal by Novo Nordisk.

With regard to the claim 'no undesirable weight gain' the Panel noted that Section 5.1 of the Levemir SPC stated 'In long-term treatment trials, fasting plasma glucose in patients with type 1 diabetes was improved with Levemir compared with NPH insulin when given as basal/bolus therapy. Glycaemic control (HbA_{1c}) with Levemir is comparable to NPH insulin, with a lower risk of nocturnal hypoglycaemia and no associated weight gain'. In the Panel's view the statement about no associated weight gain referred only to type 1 diabetics. A later statement in Section 5.1 read 'Unlike other insulins, intensive therapy with Levemir is not associated with undesirable weight gain'.

In the treatment of type 1 diabetics the majority of papers submitted by Novo Nordisk reported a small weight loss in patients treated with Levemir although one reported no weight change in patients treated with insulin detemir. With regard to type 2 diabetes, the three studies which recruited solely this group of patients all reported increased weight (0.51kg-1.2kg) in those treated with Levemir. The Panel considered that the data thus showed a difference in effect in type 1 and type 2 diabetics. The claim at issue 'no undesirable weight gain' implied that no diabetic patient, type 1 or type 2, would gain weight with Levemir and this was not so. The claim was thus inaccurate, unsubstantiated and exaggerated as alleged. The Panel ruled breaches of the Code.

Upon appeal by Novo Nordisk, the Appeal Board noted that Section 5.1, *inter alia*, stated 'Unlike other insulins, intensive therapy with Levemir is not associated with undesirable weight gain'. The Appeal Board did not consider that this statement was the same as the claim at issue 'No undesirable weight gain'; the SPC wording was clearly linked to an intensive dosing regimen.

The Appeal Board noted there was data indicating a small or no weight loss in type 1 diabetics treated with a non-intensive Levemir dosing regimen. Conversely, type 2 diabetics treated with a non-intensive regimen reported a weight increase.

The Appeal Board considered that the claim at issue 'no undesirable weight gain' implied that no diabetic patient, type 1 or type 2, would gain weight with Levemir and this was not so. No data had been submitted to show no weight gain in type 2 diabetics on a non-intensive dosing regimen of Levemir. The claim was thus inaccurate, unsubstantiated and exaggerated as alleged. The Appeal Board upheld the Panel's ruling of breaches of the Code.

Aventis stated that in order to substantiate the claim 'Levemir FlexPen (insulin detemir) predictable results day after day' which appeared as a strapline beneath the product logo on pages 1, 3 and 4 of the mailing, Novo Nordisk must be able to provide data showing 'predictability' for Levemir in subjects with both type 1 and type 2 diabetics. Novo Nordisk had not provided Aventis with such data. It therefore alleged that this claim was inaccurate, unsubstantiated and exaggerated.

The Panel noted that Section 5.1 of the Levemir SPC stated that 'The time action profile of insulin detemir is statistically less variable than for NPH insulin as seen from the within-subject coefficients of variation (CV) for the total and maximum pharmacodynamic effect'. The CVs for Levemir were 27% and 23% respectively. The SPC referred to a 'more reproducible absorption and action profile of insulin detemir compared to NPH insulin'. It was also stated that 'Lower day-to-day variability in FPG was demonstrated during treatment with Levemir compared to NPH in long-term clinical trials'. There was no statement that Levemir was predicable *per se*.

With regard to published data in type 1 diabetics, it had been demonstrated that although there was less within-person variability with Levemir than with NPH insulin there was, nonetheless some variability. Similar results had been reported in patients with type 2 diabetes.

The Panel considered that whilst the concept of predictability of response to insulin was understood by health professionals the claim at issue 'predictable results day after day' implied that there would be no within-person variation in glycaemic control with Levemir, which was not so. The claim was a strong, absolute claim which was not supported by the data. The Panel thus considered that the claim was misleading, unsubstantiated and exaggerated as alleged; breaches of the Code were ruled.

Upon appeal by Novo Nordisk, the Appeal Board noted Section 5.1 of the Levemir SPC and the published data in type 1 and type 2 diabetics. The Appeal Board considered, however, that the concept of predictability of response to insulin was understood by health professionals and thus the claim at issue 'predictable results day after day' would not be interpreted as a claim of absolute predictability. Although the claim was a strong claim, it was substantiable both by the SPC and by published data. The Appeal Board thus considered that the claim was not misleading or exaggerated as alleged; no breaches of the Code were ruled.

Aventis stated that the use of the broad claims highlighted above suggested that Levemir would be appropriate for use in children and adolescents. The SPC stated that 'The efficacy and safety of Levemir have not been studied in children and adolescents'. Aventis alleged that these claims were outside the terms of the marketing authorization and inconsistent with the SPC.

The Panel noted that Section 4.2 of the Levemir SPC stated that the efficacy and safety of Levemir had not been studied in children and adolescents. Section 5.2 stated that the pharmacokinetics of Levemir were investigated in children (6-12 years) and adolescents (13-17 years) and compared to adults with type 1 diabetes. There was no clinically relevant difference in pharmacokinetic properties. As the pharmacokinetics had not been studied extensively in these populations it was advised to monitor plasma glucose closely in these populations. The

Panel noted that the use of Levemir was not contraindicated in children.

The Panel noted that neither the front cover nor inside pages of the mailing referred to the use of Levemir in children or adolescents. The graphics did not show a child or adolescent. In the context in which they were made, the Panel thus did not consider that the claims at issue above were inconsistent with the marketing authorization on this point as alleged. No breach of the Code was ruled.

Aventis was unsure of the exact meaning of an unreferenced claim '…in a reliable pen'. Either reliable was used as an absolute term to suggest that Levemir was 100% reliable, in which case it seemed highly unlikely that Novo Nordisk had data to support the claim thus the claim was likely to be inaccurate, unsubstantiable and exaggerated. Alternatively, 'reliable' was used as a relative term to suggest that Levemir was more reliable than an unspecified comparator. If this was the intention, the claim was at best a hanging comparison. The claim was alleged to be ambiguous.

The Panel noted Novo Nordisk's submission that '… in a reliable pen' referred to FlexPen as a delivery system in relation to its accuracy, safety and failure rate. Readers would assume that the claim referred to the delivery system ie the pen. Data relating to the use of the pen with other insulins would thus be relevant and was provided. The Panel did not consider that the claim suggested that Levemir FlexPen was 100% reliable as alleged by Aventis, ie that no malfunctions or failures had ever been recorded. The Panel did not consider the claim was misleading, incapable of substantiation or exaggerated as alleged; no breach of the Code was ruled.

The Panel did not consider that the phrase was directly or indirectly comparative; it was not a hanging comparison as alleged; no breach of the Code was ruled.

Aventis alleged a breach of the Code as it had asked Novo Nordisk for data to substantiate a number of claims but Novo Nordisk failed to provide it.

The Panel noted Novo Nordisk's response that as the material at issue was substantiated by the published cited references, Novo Nordisk did not send these to Aventis and the item was being withdrawn. The Panel considered that these reasons were inadequate; substantiation had to be provided irrespective of whether the references were publicly available or whether the item was to be withdrawn. A breach of the Code was ruled.

Aventis Pharma Ltd complained about a four page mailing (ref DM/073/0504) for Levemir (insulin detemir) issued by Novo Nordisk Limited. Aventis supplied Lantus (insulin glargine). Aventis noted that similar claims appeared in other promotional items.

1 Claims 'a more predictable profile than glargine and NPH [neutral protamine hagedom]'; 'fewer nocturnal hypoglycaemic events than NPH'; 'more effective glycaemic control than NPH' and 'no undesirable weight gain'

These claims appeared as bullet points on the front page beneath the heading 'Levemir FlexPen – a new basal insulin analogue for people with diabetes who need'.

COMPLAINT

Aventis stated that the phrase '…for people with diabetes…', which appeared above the bullet points at issue, clearly suggested that Levemir FlexPen was an appropriate treatment for all individuals with diabetes who had the four requirements.

There were different classification of diabetes, the best known being types 1 and 2 which were recognised as being distinct pathological entities. Therefore, in order to substantiate each of the four claims, Novo Nordisk must be able to provide data for Levemir in both type 1 and type 2 diabetics. Aventis noted that the references given for each claim only referred to studies conducted in type 1 diabetics.

Novo Nordisk had been unable to provide evidence to substantiate these claims for Levemir in all people with diabetes. Aventis therefore alleged that the four claims for Levemir FlexPen were inaccurate, unsubstantiated and exaggerated, in breach of Clauses 7.2, 7.4 and 7.10 of the Code.

RESPONSE

Novo Nordisk explained that whilst type 1 and type 2 diabetes had different characteristics, they also shared many common features. First and foremost there was failure of endogenous insulin production by the pancreas. Secondly, type 1 diabetics were treated with insulin early in their disease; type 2 diabetics were also treated with insulin, although later in the disease progression. To all intents and purposes, the types of insulin used in the management of type 1 diabetics were also the same types of insulins used in the management of type 2 diabetics. Novo Nordisk drew attention to some examples of summaries of product characteristics (SPCs) for different insulins marketed in the UK by Lilly, Aventis and Novo Nordisk. All carried the same licensed indication: 'the treatment of diabetes mellitus'. The regulatory authorities had sanctioned, over many years, licences for insulin with no specific reference being made to the type of diabetes. The same held true for insulin glargine (Lantus) marketed by Aventis.

Turning to the specific allegations:

A more predictable profile than glargine and NPH

In insulin research conducted by academia and pharmaceutical companies, including Novo Nordisk and Aventis, pharmacodynamic studies using euglycaemic clamp techniques were performed in type 1 diabetes. Such pharmacodynamic studies tended not to be conducted in patients with type 2 diabetes for a variety of reasons, one of which being the existence of varying degrees of insulin resistance.

The definitive Textbook of Diabetes by Pickup and Williams stated 'The GIR [glucose infusion rate] thus constitutes a quantitative parameter reflecting the metabolic activity of the investigated insulin

preparations over time'. It further stated that 'The GIR thus also constitutes a measure of the net biological effect of the insulin' and that 'This experimental approach is now regarded as the gold standard for quantifying the pharmacodynamic properties of insulin preparations and insulin administration techniques'. No distinction between type 1 and type 2 diabetes was made, as such pharmacodynamic properties measured were the properties of the insulin, regardless of whether the study was conducted in type 1 or type 2 diabetes.

In fact pharmacodynamic studies were sometimes conducted in healthy volunteers, and the results – ie the properties of the insulins – were extrapolated to people with diabetes in general. One such example was NovoMix 30, an insulin marketed by Novo Nordisk licensed for the 'treatment of diabetes mellitus'. The properties of NovoMix 30 were established using pharmacodynamic studies in healthy volunteers and the regulatory authorities clearly accepted this extrapolation as the basis of its licensed indication as shown in its SPC.

The Levemir SPC stated its indication as 'Treatment of diabetes mellitus', with no distinction between the types of diabetes and further stated that 'The time action profile for insulin determir is statistically significantly less variable than for NPH insulin…'. The regulatory authorities clearly agreed with Novo Nordisk that insulin properties such as less variability – or more predictability – could be extrapolated from type 1 to type 2 diabetics.

The same study which had been published in full by Heise *et al* (2004) included data on insulin glargine and the results of the study clearly showed lower within-subject variability for Levemir compared with NPH and with insulin glargine (coefficient of variation, CV, for GIR-$AUC_{(0\text{-}24\ h)}$ was 27% for Levemir, 68% for NPH insulin and 48% for insulin glargine).

The Scottish Medicine Consortium (SMC) in its recent recommendation to Scottish NHS Trusts on Levemir, advised that 'Insulin detemir is an acceptable basal insulin for patients with diabetes mellitus… reduced intra-individual variation in glycaemic profile for insulin detemir compared with established insulins', again making no distinction between type 1 and type 2 diabetes.

The prevailing body of specialist medical opinion was such that this type of data on properties of insulin (less variation or better predictability) could be extrapolated from type 1 to type 2 diabetes, and such properties held true as they were intrinsic to insulins rather than to the type of diabetes.

Heise *et al* was clearly cited in the mailing at issue and also in promotional materials DM/070/0504, DM/090/0604 and DM/080/0604.

It was a well-known common practice, accepted by the regulatory authorities, that properties of insulins elucidated in pharmacodynamic studies performed in healthy volunteers and type 1 diabetics could be used to extrapolate such properties to type 2 diabetics. This was the basis on which licences for insulins were granted, including Levemir and Aventis' insulin glargine.

Further supporting evidence in type 1 diabetics came from a comparison of NPH and insulin detemir in which Home *et al* (2004) reported that 'Within-person between-day variation in self-measured prebreakfast plasma glucose was lower for both detemir groups ($p<0.001$)'. In type 1 diabetes, Hermansen *et al* (2004a) reported that 'Within-person day-to-day variation in plasma glucose was lower with insulin detemir/insulin aspart than with NPH insulin/regular human insulin (SD: 2.88 vs 3.12mmol/l; $p<0.001$)'. In type 1 diabetics, Russell-Jones *et al* (2004a) reported that, compared with NPH insulin 'Day-to-day variability in self-measured fasting blood glucose was lower with insulin detemir (SD 2.82 vs 3.60mmol/l, $p<0.001$)'.

In type 2 diabetics, Haak *et al* (2003) reported that, compared with NPH, 'Treatment with IDet [insulin detemir] resulted in a lower within-subject variation in self-measured fasting blood glucose compared to NPH (SD=1.3 vs 1.4mM, $p=0.02$)'.

New evidence emerged with on-going research. Novo Nordisk cited the following newly published data to further support its claims: in type 2 diabetes, Raslova *et al* (2004) reported that '… IDet [insulin detemir] + IAsp [insulin aspart] was associated with a significantly lower within-person variation in self-measured fasting plasma glucose (FPG) (SD: 1.20 versus 1.54mmol/l, $p<0.001$) … than with NPH + HSI [human soluble insulin]'.

Garber *et al* (2004) reported, in a meta-analysis combining both type 1 and type 2 diabetes, that 'Day-to-day within-person variability in self-measured FBG [fasting blood glucose] was significantly lower with insulin detemir than with NPH after an overnight fast' (standard deviation, sd, of 2.55 for Levemir versus 3.06 for NPH, $p<0.0001$). Russell-Jones *et al* (2004b) reported, in another meta-analysis of both type 1 and type 2 diabetes, that there was significant reduction in blood glucose variability with insulin detemir versus NPH insulin. These results were conclusively demonstrated using state-of-the-art 24-hour continuous glucose monitoring.

Fewer nocturnal hypoglycaemic events than NPH

This claim narrowed down to a comparison between Levemir and NPH. Again the broad principles listed above regarding the types of diabetes held true.

The SMC, in its advice regarding the use of Levemir, recommended that 'Its use should be targeted on patients attempting to achieve better hypoglycaemic control', again making no distinction between type 1 and type 2 diabetes.

Raslova *et al* (2004) in a study in type 2 diabetes reported that the relative risk of nocturnal hypoglycaemia was lower with insulin detemir compared with NPH insulin, with a relative risk of 0.62, in other words there was a risk reduction of 38%. In another study in type 2 diabetes, Hermansen *et al* (2004b) reported that 'The risk of overall and nocturnal hypoglycaemia was 47% and 55% lower with insulin detemir than with NPH insulin ($p<0.001$)'.

With regard to type 1 diabetes Home *et al* reported a 53% reduction in nocturnal hypoglycaemia with

[Levemir compared with NPH] where Levemir was administered in the morning and at bed time (IDet morn+bed). Russell-Jones *et al* reported that there was a 26% reduction in the relative risk of nocturnal hypoglycaemia in the insulin detemir treatment arm. Hermansen *et al* reported that with insulin detemir/insulin aspart, nocturnal hypoglycaemia was reduced by 55% (p<0.001) compared with NPH regular human insulin. The above references were cited in the mailing at issue. Vague *et al* (2003) and De Leeuw *et al* (2002), also both cited in the mailing, reported that insulin detemir lowered the risk of nocturnal hypoglycaemia by 34% (p<0.005) and 32% (p=0.016) respectively compared with NPH. Standl *et al* (2002), again cited in the mailing, reported a trend towards lower risk of hypoglycaemia during the night (relative risk (detemir/NPH) = 0.71, p=0.067).

In a meta-analysis which combined data from type 1 and type 2 diabetes, Heller *et al* (2004) concluded 'that the risk of minor hypoglycaemia with insulin detemir is lower than with NPH, both overnight [nocturnal] and over 24h'. Nattrass *et al* (2004), in another meta-analysis of type 1 and type 2 diabetes, concluded that 'Significantly fewer nocturnal hypoglycaemic episodes registered by symptoms only were reported with insulin detemir than with NPH insulin'.

More effective glycaemic control than NPH

Again the broad principles above regarding distinction between types of diabetes applied.

Novo Nordisk stated that many of its studies showed a lower fasting plasma glucose in patients treated with Levemir compared with patients treated with NPH. For instance, in type 1 diabetes, Home *et al* reported that fasting plasma glucose was lower by 1.5mmol/l (p=0.004) with insulin detemir administered 12 hourly (IDet $_{12hr}$) than with NPH; fasting plasma glucose was lower by 2.3mmol/l, p<0.001) with insulin detemir administered morning and bed-time (IDet $_{m+b}$) than with NPH. Russell-Jones *et al* (2004a) reported that FPG (fasting plasma glucose) was 1.16mmol/l lower with insulin detemir than with NPH (p=0.001).

Turning to HbA_{1c}, another measure of glycaemic control. Home *et al* reported that HbA_{1c} in patients treated with Levemir (pooled insulin detemir groups) was 0.18% lower than for the NPH group (p=0.027). Hermansen *et al* (2004a) reported that glycaemic control with insulin detemir/insulin aspart was improved in comparison with NPH insulin/regular human insulin (HbA_{1c}: 7.88% vs 8.11%, mean difference: – 0.22%; p<0.001).

Combining fasting plasma glucose (FPG) and HbA_{1c}, Garber *et al* (2004) reported in a meta-analysis that combined data from 6 multi-national studies, including data for type 1 and type 2 diabetes, that 'insulin detemir provides better glycaemic control, as measured by HbA_{1c} and FPG … compared to NPH insulin in people with diabetes'. The authors made no distinction between the types of diabetes as the results encompassed both sub-groups. In this analysis, FPG was 1.1mM lower with insulin detemir than NPH insulin; HbA_{1c} was 0.09% lower with insulin detemir than NPH insulin. 95% confidence intervals (CI) for both results indicated that the results were robust and statistically significant.

No undesirable weight gain

The SPC for Levemir stated that 'unlike other insulins, intensive therapy with Levemir is not associated with undesirable weight gain'.

There was a large body of evidence in both type 1 and type 2 diabetes to support this claim. In type 1 diabetes Home *et al* reported that 'The NPH group gained weight during the study, but there was no change in weight in either of the insulin detemir groups (IDet $_{12\ hr}$ vs NPH, – 0.8kg, p= 0.006; IDet $_{m+b}$ vs NPH, – 0.6kg, p=0.040)'. Russell-Jones *et al* reported that 'Gain in body weight was significantly lower after 6 months with insulin detemir than with NPH (– 0.54kg difference, p=0.024)'. Hermansen *et al* (2004a) reported that 'body weight (adjusted for baseline and change in HbA_{1c}) was 1kg lower with insulin detemir/insulin aspart than with NPH insulin/regular insulin, p<0.001)'. Vague *et al* reported that body weight was significantly lower with insulin detemir at the end of the trial (p<0.001), (patients on insulin detemir lost 0.2kg while patients on NPH insulin gained 0.7 kg). De Leeuw *et al* reported that body weight was significantly lower with insulin detemir than with NPH (71.5 kg vs 72.8 kg; p<0.001). Standl *et al* reported that a weight loss of 0.3kg was observed in the insulin detemir group, compared with a weight gain of 1.4kg with the NPH insulin group (p=0.002). In type 2 diabetes, Haak *et al* reported that body weight was significantly lower in the insulin detemir group than in the NPH group (p=0.02), with a weight increase of 0.9kg in the insulin detemir group vs an increase of 1.6kg in the NPH group. Raslova *et al* reported that a lower body weight gain was achieved with insulin detemir compared with NPH insulin (0.51kg vs 1.13kg, p=0.038).

In a meta-analysis of type 1 and type 2 diabetes, Garber *et al* reported that 'body weight was significantly lower at the end of treatment with insulin detemir compared with NPH insulin' (weight difference 0.74kg in favour of insulin detemir, p<0.0001. Again these results made no distinction as to sub-types of diabetes.

PANEL RULING

The Panel noted the allegation that the claims at issue were inaccurate, unsubstantiable and exaggerated as Novo Nordisk had not provided data for Levemir in type 2 diabetics. The studies cited in the mailing were in type 1 diabetics.

The Panel noted Novo Nordisk's submission that the prevailing body of specialist medical opinion was such that certain data on properties of insulin (such as variation or predictability) could be extrapolated from type 1 to type 2 diabetes and such properties held true as they were intrinsic to insulins rather than the type of diabetes.

The Panel noted that Section 4.1 of the Levemir SPC stated that it was indicated for the treatment of diabetes mellitus; Section 4.1 did not differentiate

between type 1 and type 2 diabetes. Section 4.4 discussed hypoglycaemia in relation to type 1 diabetes and the activity profile of Levemir in type 1 diabetics was referred to in relation to Levemir's pharmacodynamic properties.

The Panel also noted that Section 4.1 of the SPCs for other insulins, such as NovoMix Penfill and FlexPen, Actrapid (vial, Penfill and Novolet), Mixtard (vial, Penfill, Novolet), Insulatard (vial, Penfill, Novolet, Imolet, Flexpen) all referred to the treatment of diabetes mellitus and similarly did not differentiate between type 1 and type 2 diabetes.

A more predictable profile than glargine and NPH

The Panel noted that Section 5.1 of the Levemir SPC stated that the time action profile of insulin detemir was statistically significantly less variable than for NPH insulin as seen from the within-subject coefficients of variation for the total and maximum pharmacodynamic effect. There was no comparable statement in the SPC with regard to insulin glargine.

The Panel noted that Novo Nordisk had submitted a number of studies to support the statement in the SPC with regard to NPH both in type 1 diabetics (Hermansen *et al* 2004a; Home *et al*; Russell-Jones *et al* 2004a and Vague *et al*) and in type 2 diabetics (Hermansen *et al* 2004b and Raslova *et al* 2004). Two papers had been submitted comparing insulin detemir and insulin glargine (Heise *et al* 2003 which appeared to be the initial poster presentation of the later full paper Heise *et al* 2004). The reports compared the within-subject variability of the glucose lowering effect of the insulins using 51 type 1 diabetics of whom 18 were on insulin detemir, 17 on NPH insulin and 16 on insulin glargine. The results suggested that insulin detemir had a significantly more predictable glucose-lowering effect than both NPH insulin and insulin glargine ($p<0.001$). In the Panel's view, however, the size of the study was too small to be used as the sole basis for a comparable efficacy claim vs insulin glargine with regard to type 1 diabetics. No data in type 2 diabetics had been provided. The Panel considered that it had not been established that Levemir had a more predictable profile than glargine and in that regard the claim at issue was inaccurate, unsubstantiated and exaggerated as alleged. The Panel ruled breaches of Clauses 7.2, 7.4 and 7.10 of the Code.

Fewer nocturnal hypoglycaemic events than NPH

The Panel noted that Section 5.1 of the Levemir SPC stated, with regard to type 1 diabetes, that there was a lower risk of nocturnal hypoglycaemia with Levemir than with NPH insulin. It was further stated that analyses of nocturnal hypoglycaemia in type 1 diabetes showed a significantly lower risk of minor nocturnal hypoglycaemia than with NPH insulin, whereas no difference was seen with type 2 diabetes.

The Panel noted that Novo Nordisk had submitted a number of papers to support the statement in the SPC with regard to type 1 diabetics (Hermansen *et al* 2004a; Home *et al* and Vague *et al*). Only two papers had been submitted which dealt solely with the treatment of type 2 diabetics (Hermansen *et al* 2004b and Raslova *et al*). Hermansen *et al* (2004b) reported that the risk of nocturnal hypoglycaemia was reduced by 55% in patients treated with insulin detemir (n=237) compared with NPH-treated patients (n=238) ($p<0.001$). Raslova *et al* reported a 38% decrease in the risk in patients treated with insulin detemir (n=185) compared with NPH-treated patients (n=193) but the results were not statistically significant.

On balance the Panel thus considered that there was insufficient data to claim that all diabetics treated with insulin detemir would have fewer nocturnal hypoglycaemic events than if they had been treated with NPH. There was the data to show that this was the case in type 1 diabetics but insufficient data in type 2. The Panel noted the SPC statement in this regard. The Panel thus considered that the claim was inaccurate, misleading and exaggerated as alleged. Breaches of Clauses 7.2, 7.4 and 7.10 were ruled.

More effective glycaemic control than NPH

The Panel noted that Section 5.1 of the Levemir SPC stated 'In long-term treatment trials, fasting plasma glucose in patients with type 1 diabetes was improved with Levemir compared with NPH insulin when given as basal/bolus therapy. Glycaemic control (HbA_{1c}) with Levemir is comparable to NPH insulin, with a lower risk of nocturnal hypoglycaemia and no associated weight gain'. The Panel thus considered that, in the context in which it appeared, the statement about glycaemic control related only to type 1 diabetics.

The Panel considered that the majority of readers would assume that 'glycaemic control' referred to the measurement of HbA_{1c} as implied in the Levemir SPC. The SPC stated that, in type 1 diabetics, glycaemic control with Levemir was comparable to NPH insulin and the majority of the papers submitted by Novo Nordisk supported this statement (De Leeuw *et al*; Russell-Jones *et al* 2004a); Standl *et al* and Vague *et al*). Only two studies, Hermansen *et al* (2004a) and Home *et al*, reported statistically significant advantages for insulin detemir compared with NPH insulin. The balance of evidence was thus that the two insulins were comparable in type 1 diabetics.

With regard to type 2 diabetics only two studies, Hermansen *et al* (2004b) and Raslova *et al* had compared insulin detemir and NPH insulin in this group. Both groups reported that, in terms of HbA_{1c}, the two insulins were comparable.

The Panel thus considered that, the claim 'More effective glycaemic control than NPH' was inaccurate, misleading and exaggerated as alleged. Breaches of Clauses 7.2, 7.4 and 7.10 were ruled. The Panel was also concerned that the claim was inconsistent with the particulars listed in the Levemir SPC and asked that Novo Nordisk be advised of this concern.

No undesirable weight gain

The Panel noted that Section 5.1 of the Levemir SPC stated 'In long-term treatment trials, fasting plasma glucose in patients with type 1 diabetes was improved with Levemir compared with NPH insulin when given as basal/bolus therapy. Glycaemic control

(HbA_{1c}) with Levemir is comparable to NPH insulin, with a lower risk of nocturnal hypoglycaemia and no associated weight gain'. In the Panel's view the statement about no associated weight gain referred only to type 1 diabetics. A later statement in Section 5.1 read 'Unlike other insulins, intensive therapy with Levemir is not associated with undesirable weight gain'.

In the treatment of type 1 diabetics the majority of papers submitted by Novo Nordisk reported a small weight loss in patients treated with Levemir (Hermansen *et al* 2004a; Russell-Jones *et al* 2004a; Standl *et al* and Vague *et al*). Home *et al* reported no weight change in patients treated with insulin detemir.

With regard to type 2 diabetes, the three papers studies which recruited solely this group of patients (Haak *et al*; Hermansen *et al* 2004b and Raslova *et al*) all reported increased weight in those treated with Levemir (0.9kg, 1.2kg and 0.51kg respectively).

The Panel considered that the data thus showed a difference in effect in type 1 and type 2 diabetics. The claim at issue 'no undesirable weight gain' implied that no diabetic patient, type 1 or type 2, would gain weight with Levemir and this was not so. The claim was thus inaccurate, unsubstantiated and exaggerated as alleged. The Panel ruled breaches of Clauses 7.2, 7.4 and 7.10 of the Code.

APPEAL BY NOVO NORDISK

With regard to the extrapolation between type 1 and type 2 diabetes, Novo Nordisk submitted that advanced type 2 diabetes, where insulin was mostly used, shared a similar pathophysiology to type 1 diabetes characterised by absolute insulin deficiency. Nevertheless, there were major differences in the aetiology and other differences in the pathophysiology of these two types of diabetes mellitus, and endpoints achieved in a study in one should not necessarily become expectations of the other. For example, the ability to aggressively titrate an insulin dose to achieve a mean HbA_{1c} of less than 7% in a clinical trial setting in a cohort of poorly-controlled insulin-naïve patients with type 2 diabetes, could not imply that similar targets could be achieved in poorly-controlled type 1 patients, because in the latter the risk of hypoglycaemia was much greater.

Novo Nordisk submitted that it was important, when assessing new therapies, to recognise that type 1 diabetics were more 'sensitive' to the effects of an insulin preparation than type 2 diabetics. This was because for type 1 diabetics, aspects of metabolic (most notably, glycaemic) control were totally dependent on the pharmacokinetic and pharmacodynamic properties of the exogenous insulin, there being little or no endogenous insulin secretion. Furthermore, type 1 diabetics were far less likely to be insulin resistant than were type 2 diabetics. This meant that differences in the pharmacological properties of insulins were more readily distinguishable in type 1 diabetics. For example, small differences in the kinetic profiles of two different insulin preparations might result in a significantly different risk of hypoglycaemia in a clinical trial in type 1 diabetics, whereas such a difference might not be detectable in a trial of similar size in type 2 diabetics.

Novo Nordisk submitted that because C-peptide negative type 1 diabetics had no endogenous insulin production they were always used to study and define the properties of insulins because there was no endogenous insulin response to cloud the picture. Therefore any physiological action must be due to the exogenous insulin under study. The regulatory authorities insisted that this patient group was studied because most information was gained this way.

Novo Nordisk noted that many between-treatment differences in the 'behaviour' of an insulin in type 1 diabetics (eg variability, hypoglycaemia risk) were also likely to apply in type 2 diabetics if these arose from inherent pharmacokinetic properties of the insulins tested. However, while relative risk reductions might be preserved, absolute risk reduction (effect size) might be reduced in type 2 diabetics such that larger cohorts were required to illustrate such differences statistically. This disparity was one of the reasons why the Diabetes Control and Complications Trial (DCCT) in type 1 diabetes recruited 1441 patients to evaluate the impact of intervention and outcome, whereas the corresponding United Kingdom Prospective Diabetes Study (UKPDS) in type 2 diabetes recruited 4209 patients.

Novo Nordisk submitted that evaluation of insulin products could thus be achieved far more accurately and efficiently in type 1 diabetes, so it was surely not surprising that, in common with other insulin manufacturers, Novo Nordisk had conducted much of its initial research on Levemir in type 1 diabetics. This practice had been sanctioned by the licensing authorities over many years, with generally no distinction made between type 1 and type 2 diabetes in the licence indication granted. Consequently, all insulins were licensed simply for 'the treatment of diabetes mellitus'.

Novo Nordisk submitted that a discrepancy in effect size raised the question of whether a reduction in the absolute advantage in type 2 diabetes was of clinical relevance. Here, absolute risks and risk reductions must be balanced against a much larger population size. For example, a 40% reduction in risk of nocturnal hypoglycaemia might involve relatively few events per patient per year, but in the context of a very large population the impact on morbidity and mortality could nevertheless be considerable.

Novo Nordisk submitted that there were instances where extrapolations could be confidently made when these pertained to pharmacological properties that were largely independent of disease pathophysiology. Thus, two insulins shown to differ in the predictability of their absorption profile in volunteer studies would show similar differences in both type 1 and type 2 diabetics because the disparity in their kinetic properties was unlikely to be influenced by the pathophysiology of diabetes. If such inherent pharmacological differences were shown to underlie a between-treatment difference in the risk of hypoglycaemia in type 1 diabetes, then they should

also convey a risk reduction for hypoglycaemia in type 2 diabetes. The absolute risks would, of course, be different, as explained above, but a relative risk reduction remained an inherent property of the insulin's pharmacology. It was on this basis that the regulatory authorities had agreed various statements in the Levemir SPC (as well as for other insulins on the market). The Panel appeared to accept this point in principle, but nevertheless ruled in apparent contradiction on a number of occasions.

Novo Nordisk considered each specific claim in turn:

A more predictable profile than glargine and NPH

Novo Nordisk submitted that the claim 'A more predictable profile than glargine and NPH' was not in breach primarily because it was directly and unambiguously substantiated by the largest glycaemic clamp study ever reported. The predictable profile of Levemir resulted from inherent pharmacological properties of the medicine that were independent of the pathophysiology of diabetes, and which hence underpinned clinical advantages in both type 1 and type 2 diabetes.

The significance of the claim 'A more predictable profile than glargine and NPH' stemmed from that fact that traditional basal insulins provided a limited consistency in the blood glucose-lowering time-action profile from injection to injection. Absorption rate into the circulation was variable, and unexpected highs or lows (even following a single injection) could cause episodes of hypo- or hyperglycaemia in a diabetic, thereby compromising metabolic control and putting the person at risk of hypoglycaemia. Blood glucose variability had been shown to correlate with adverse outcomes such as hypoglycaemic risk (Moberg *et al* 1994) and mortality risk (Muggeo *et al* 2000). Therefore, a more predictable profile was clinically highly desirable.

Novo Nordisk noted that the Panel had accepted that the claim of increased predictability in comparison to NPH was well substantiated for Levemir in type 1 and type 2 diabetes. However, the Panel ruled that the claim in relation to insulin glargine was not substantiated on the grounds that Heise *et al*, which used glycaemic clamp methods, was too small; it was however the largest study of its type ever undertaken.

Novo Nordisk submitted that it was widely acknowledged that the glucose infusion rate (GIR) method, as used here, was the best method available to quantify the blood glucose-lowering potential of an insulin preparation and also for measuring variability (and hence predictability) of the glucose-lowering profile of that insulin. In fact, GIR profiling during clamped glycaemia and fasting was the only methodology that directly and accurately measured this property. Clamp studies enabled the glucose-lowering properties of an insulin to be observed safely ie without putting the subject at risk of hypoglycaemia.

Novo Nordisk stated that clamp studies could appear to non-specialists to be of small size, but this was because they posed enormous practical difficulties. For each clamp procedure in Heise *et al* the subject was required to fast overnight before connection to a glucose controlled insulin infusion system at least 4 hours before trial drug administration. After this, the 24-hour glucose infusion procedure was begun. Throughout all of this, each subject had to remain fasting and in a supine position while enduring intravenous infusions of insulin and/or glucose and serial blood sampling. As the study repeated these procedures on 4 occasions for each of 51 patients completing the study then over 200, 24 hour glycaemic clamps, were performed, making this the largest glycaemic clamp study ever reported. For comparison, another clamp study which evaluated the pharmacological profile of insulin glargine in relation to NPH, ultralente and a continuous subcutaneous infusion of insulin lispro attempted only 80 clamps in 20 patients (Lepore *et al* 2000).

Heise *et al* showed that Levemir had a lower within-patient variability (in other words it was more predictable) than NPH insulin and insulin glargine (coefficient of variation for GIR-$AUC_{(0\text{-}24h)}$ was 27% for Levemir, 68% for NPH insulin and 48% for insulin glargine).

Novo Nordisk submitted that in addition, achieving statistical significance with an appropriate power based on a relatively small sample size suggested that the difference in effect was really substantial. Thus, regulatory authorities routinely accepted the findings of what might seem like small clamp studies in recognition of the practical difficulties involved and the validity of this type of study when statistically significant findings were made.

Novo Nordisk submitted that notwithstanding that aspects of the pharmacological profile dependent on absorption would be unchanged in type 2 diabetes, it acknowledged that a similar study to assess variability directly in type 2 diabetes would be the ideal. Clamp studies in type 2 diabetes were fraught with even more methodological difficulties due to the problems of interpretation posed by heterogeneity in preserved endogenous insulin secretion and insulin resistance. Nevertheless, the results of a smaller, unpublished dose-response clamp trial comparing Levemir with NPH insulin with multiple administrations of the insulins in type 2 diabetics agreed with the findings in type 1 diabetes (data on file). The trial was designed to compare molar dose potency and was not powered to evaluate variability, but Levemir was nevertheless associated with non-significant relative reductions of 28% and 48% for variability in the parameters of AUC_{GIR} and GIR_{Max}, respectively (data on file).

Novo Nordisk noted that there were firm a priori reasons for expecting Levemir to be intrinsically more predictable than other long-acting insulins. It was well recognised that much variability arose as a result of inconsistent resuspension prior to injection and chaotic precipitation/re-dissolution following injection compounded by variable blood perfusion of the injection depot (Kurtzhals 2004). Insulin detemir was the only basal insulin that remained as a solute throughout these processes, and its albumin binding properties had been calculated to buffer the effects of changes in absorption rate arising from variable blood flow (Kurtzhals and Colding-Jorgensen 2004; Kurtzhals).

Novo Nordisk acknowledged that it was important to consider how predictability in the pharmacological profile would be manifest clinically and to establish through clinical data that meaningful patient benefits were likely. There were a number of ways in which reduced variability could be detected in clinical studies. These included a relative reduction in the coefficient of variation (CV) (or of standard deviation (SD)) in a time point of glucose measurement (eg fasting blood glucose (FBG)), and a reduction in the extent to which blood glucose fluctuated during continuous glucose monitoring (CGM). These findings had been made in nearly every case where they had been investigated. To illustrate this Novo Nordisk reproduced a figure of CGM data (Russell-Jones 2004a), and a summary of CV and SD values from every published phase 3 study where serial FBG data were collected. Methodological details and identification numbers for all of the cited studies were provided.

Novo Nordisk submitted that the summary showed a significant advantage for Levemir in nine of the eleven studies (with another one returning a p value of 0.055), while the CGM data showed more constant mean BG levels during CGM with Levemir than NPH. Moreover, Russell-Jones *et al* (2004b) recently reported a meta-analysis of CGM data from five phase 3 trials involving type 1 (n=590) and type 2 (n=168) diabetics. Here, Levemir was again associated with significant reductions in 24-hour and nocturnal blood glucose fluctuation, and in the duration and frequency of excursions to levels below 4mmol/l, indicating a tendency to produce much more constant blood glucose time-curves.

Novo Nordisk submitted that a recent meta-analysis explored the relationship between coefficient of variation in FBG and risk of hypoglycaemia in type 1 diabetes (Heller *et al* 2004a) and this showed a positive correlation, indicating that the relatively reduced variability in FBG seen with Levemir could explain just over 50% of a relative risk reduction for hypoglycaemia. Thus, the 'more predictable profile' of Levemir seemed to have real clinical significance.

Fewer nocturnal hypoglycaemic events than NPH

Novo Nordisk submitted that the claim 'Fewer nocturnal hypoglycaemic events than NPH' was not in breach because it was substantiated by numerous clinical trials and was a consistent observation across the phase 3 programme. Aventis had cited a lack of evidence in type 2 diabetes, but Novo Nordisk contended that the claim had been fully substantiated in a treat-to-target protocol trial in type 2 diabetes where most patients achieved HbA_{1c} <7.0%. At this level of glycaemic control, nocturnal hypoglycaemia was sufficiently frequent to allow proper statistical evaluation (hypoglycaemia was less frequent in type 2 than in type 1 diabetes) and Levemir was associated with a 55% relative risk reduction vs NPH ($p<0.001$).

Novo Nordisk noted that hypoglycaemia was unpleasant, potentially fatal and was the most feared adverse event of insulin therapy. It was a major barrier to the initiation of insulin in type 2 diabetics, and to the intensification of insulin in type 1 or 2 diabetes (Korytkowski 2002; Mathieu 2004).

Additionally, hypoglycaemia was the major limiting factor in the achievement of good metabolic control in insulin-treated diabetes (Cox *et al* 1987; Irvine and Saunders 1989; Davis and Alonso 2004). Daytime hypoglycaemia generally evoked warning symptoms enabling corrective action, but at night-time there might be no awareness of an impending episode, and third party assistance might not be readily available. Thus, nocturnal hypoglycaemia was especially feared and distressing.

Novo Nordisk submitted that furthermore, differences in nocturnal hypoglycaemia better illustrated differences between basal insulins as this period was generally not complicated by the influence of mealtime insulin therapies. Levemir had been associated with relative risk reductions for nocturnal hypoglycaemia (vs NPH) in nearly all clinical studies, and in some cases the risk reduction had exceeded 50%. This claim represented one of the greatest clinical benefits of the product. However, the Panel found the claim in breach of the Code on the grounds of insufficient data in type 2 diabetes. Novo Nordisk in this regard noted the following:

Firstly, the original phase 3 trials were conducted as non-inferiority protocol trials with efficacy as the primary endpoint, in accordance with the requirements of regulatory authorities. Hypoglycaemia data were collected as secondary endpoints but the trials were not designed to be powered to detect risk reductions for hypoglycaemia. Despite this, a numerical relative risk reduction for nocturnal hypoglycaemia was found in all trials where this information was obtained, and this finding reached statistical significance in 8 of the trials.

Novo Nordisk submitted that it was true that a statistically significant risk reduction was not found in all trials in type 2 diabetes, but this was not unexpected because the absolute numbers of hypoglycaemic events were much lower in type 2 diabetes than type 1 diabetes. As a general rule, the event rate was about 10 times greater in type 1 diabetes than in type 2 diabetes. It would therefore be exceedingly difficult to demonstrate a significant p-value in type 2 diabetes when the hypoglycaemia event rate was very low in studies not powered for this difference.

Novo Nordisk submitted that the remarkable consistency of effect confirmed in a meta-analysis of six phase 3 trials involving 1872 patients treated with Levemir and 1177 patients treated with NPH insulin (Heller *et al* 2004b) meant that a claim of reduced risk of hypoglycaemia was substantiated from an up-to-date evaluation of all of the evidence. The relative risk reduction for hypoglycaemia was a result of the inherent pharmacological properties of the insulin being more suited to basal insulin supplementation than was the case for NPH (Kurtzhals and Colding-Jorgensen), and this was not affected by pathophysiology. Thus, the claim was based on well-accepted principles and a very large data set.

Novo Nordisk stated that there was also good evidence that Levemir was associated with a highly significant risk reduction for nocturnal hypoglycaemia in type 2 diabetes (Hermansen *et al* 2004b). This study

was not part of Novo Nordisk's original submission to the regulatory authorities, and hence was not referred to in the Levemir SPC. The risk of hypoglycaemia was most marked when aggressive titration was used to achieve excellent levels of glycaemic control. In an enforced treat-to-target protocol comparison with NPH, Levemir was added to oral hypoglycaemic therapy in type 2 diabetics in poor glycaemic control, and the insulin doses were aggressively titrated to the point where more than 70% of patients in both groups had achieved HbA_{1c} <7.0%. At this excellent level of control, hypoglycaemic events occurred quite commonly, affecting 30% and 47% of Levemir- and NPH-treated patients, respectively. There was a significant risk reduction for both overall (risk reduction 47%, p<0.001) and nocturnal (risk reduction 55%, p<0.001) hypoglycaemic events with Levemir. This highly significant result could not be ignored just because some other studies with low event rates due to less rigorous titration failed to reach statistical significance in a secondary endpoint for which they were not powered. Moreover, of the two remaining type 2 studies, one showed a non-significant risk reduction of 38% and the other showed a non-significant 2% increased risk, which changed to a non-significant 9% risk reduction when adjusted for HbA_{1c}. In the other studies, adjustment for HbA_{1c} did not change the relative risk reduction for nocturnal hypoglycaemia seen with Levemir. The consistency across trials was remarkable and Novo Nordisk referred to its earlier discussion of effect size in type 2 diabetes.

More effective glycaemic control than NPH

Novo Nordisk noted that the Panel ruled a breach on the basis that most clinicians would assume effective glycaemic control equated to HbA_{1c}, and that there were insufficient data in type 2 diabetes. Novo Nordisk appealed the ruling against the claim 'More effective glycaemic control than NPH', however, on the grounds that diabetes specialists would not equate 'effective glycaemic control' solely and narrowly with HbA_{1c} as suggested. Rather, the quality of glycaemic control was assessed by a raft of measures including HbA_{1c}, FPG, glucose variability and hypoglycaemic burden. All these things considered, there was no doubt that Levemir provided a more favourable balance of control and tolerability than NPH that diabetes specialists would regard as representing more effective control. Novo Nordisk submitted that it had provided data to substantiate this.

Novo Nordisk submitted that evaluation of glycaemic control should be a consideration of all parameters related to glucose lowering, including hypoglycaemic burden, fluctuations in glucose level and fixed point measurements such as fasting plasma glucose (FPG), as it was actually done in clinical practice. Glycaemic control was not universally or even widely equated solely with HbA_{1c} – certainly not among the audience for whom the promotional literature was intended ie diabetologists and physicians treating diabetics. It was well known that HbA_{1c} in itself revealed only the average level of glucose exposure over a period of some 2-3 months. Thus it was possible for two patients to have identical levels of HbA_{1c} but for one to have maintained relatively stable levels of blood glucose while the other had experienced considerable swings in glycaemia, which were known to correlate with poor outcomes. Indeed, HbA_{1c} could be lowered by most insulins but often only at the cost of a greatly increased incidence of hypoglycaemia. This situation, however, was hardly an example of *effective* glycaemic control. Thus, HbA_{1c} alone could not be considered as the definitive measure for the quality or effectiveness of glycaemic control.

Novo Nordisk submitted that the two most important diabetes outcome studies which evaluated the relationship between control and complications, the Diabetes Control and Complications Trial (DCCT) in type 1 diabetes and the UK Prospective Diabetes Study (UKPDS) in type 2 diabetes, had both employed targets based on FPG (not HbA_{1c}) as the basis for insulin dose adjustments (Holman and Turner 1988; UKPDS 1998; DCCT 1993). Although FPG only reflected the acute level of glucose control at one specific time point, the achievement of FPG values that were reliably near to normal (plus reasonable control at other time points) ultimately translated into good control overall. Thus FPG had to be considered an important indicator of glycaemic control like HbA_{1c}; both were inter-dependent. Furthermore, FPG was arguably a better test of the action of a basal insulin because it discounted to an extent the mealtime bolus elements of the regimen, which affected HbA_{1c} through their influence upon postprandial glycaemia. 'Effective glycaemic control' therefore implied a balance whereby patients were able to reach acceptable levels of HbA_{1c} and FPG with glycaemic stability without enduring unacceptable levels of side effects such as hypoglycaemia and weight gain. The consistently superior outcomes for FPG, coefficient of variation in glucose readings, hypoglycaemic risk and weight gain achieved with Levemir in comparison to NPH combined with equivalence in HbA_{1c} confirmed a profile of more effective glycaemic control.

Novo Nordisk submitted that in seven out of ten published phase 3 studies mean FPG values favoured Levemir, significantly so in 4 cases.

Novo Nordisk noted that with regard to endpoint HbA_{1c} data for all published phase 3 trials, equivalence was shown throughout (with the exception of a single type 2 study), but when considering the 'effectiveness' of control, this should be seen in the context of the consistent advantages for nocturnal hypoglycaemia, variability, FPG, and weight. In fact, recent meta-analyses (Garber *et al* 2004; Nattrass *et al* 2004) of 6 trials with similar protocols involving patients with type 1 (n=2150) or type 2 diabetes (n=899) showed a significant, albeit small, endpoint HbA_{1c} advantage for Levemir vs NPH (– 0.09%, p<0.05) coupled with a lower FPG (–1.1mmol, p<0.05) and a lower SD of FPG (2.55 vs 3.06, p<0.0001). These observations were also associated with a relative reduction in weight at endpoint (– 0.74kg, p<0.05) and a 45% reduction in minor nocturnal hypoglycaemic event rate (p<0.0001). These observations confirmed a profile of more effective glycaemic control.

No undesirable weight gain

Novo Nordisk appealed the Panel's ruling primarily because the phrase had been taken verbatim from the SPC and clinical data provided showed that it was justified in both type 1 and type 2 diabetes.

Novo Nordisk stated that weight gain in insulin-treated patients was of more than just cosmetic concern. Even in type 1 diabetes, weight gain could be excessive. In the DCCT, patients assigned to intensified insulin therapy gained an average of 4.75 kg more than those in the conventionally-treated group ($p<0.001$) over 6 years, such that many ended up well above their ideal weight, with some increasing body mass index (BMI) by >5kg/m^2 (DCCT 2001). In the DCCT, weight gain was associated with adverse changes in cardiovascular risk profile (Purnell *et al* 1998). In type 2 diabetes, patients tended to be overweight and insulin resistant at diagnosis. Insulin therapy inevitably increased weight; in UKPDS intensively treated patients gained about 3kg more than conventionally treated patients with most of this gain in the first 12 months. In some cases weight gain could be considerable. One study of only 6 months' duration documented a mean gain of nearly 9kg when patients were treated to target HbA_{1c} by insulin initiation (Henry *et al* 1993). In type 2 diabetes in particular, insulin-associated weight gain could exacerbate disease progression by increasing insulin resistance, and could be another major barrier to the initiation or intensification of insulin treatment (Korytkowski 2002).

Novo Nordisk submitted, therefore, that Levemir's unique ability to limit weight gain had attracted great clinical interest. This was also the basis upon which the regulatory authorities agreed the term '*unlike other insulins*, Levemir is not associated with undesirable weight gain' in the SPC. In fact, it was the regulatory authorities that after careful consideration of the data inserted the word 'undesirable' in this context.

Novo Nordisk submitted that in this respect, it was surprised at the Panel's ruling. The phrase 'no undesirable weight gain' appeared twice in the SPC, the first time in the context of type 1 diabetes, but the second time in a general statement applicable to both type 1 and 2 diabetes. The Panel argued that there appeared to be a difference in effect between type 1 and type 2 diabetes. In Novo Nordisk's view this was not necessarily so. While there was a consistent weight neutrality or small weight reduction in the type 1 studies and a small weight gain in the type 2 studies, this was not necessarily a reflection of differences in the patients´ type of diabetes; it might just as well reflect differences in their prior status for insulin therapy. In the type 1 studies, all patients treated with Levemir were switched from previous insulin regimens (mostly basal-bolus regimens), whereas a large proportion of the type 2 patients (notably those in Hermansen *et al* 2004b) were insulin-naïve before entry to the study. Moreover, in those type 2 studies where patients were previously insulin treated, the regimens were intensified on entry to the study. The initiation or intensification of insulin was well known to be associated with weight gain in both type 1 and type 2 diabetes (Purnell *et al*; DCCT; UKPDS), so it was remarkable that in every clinical trial Levemir had resulted in significantly less weight gain than its comparator, and, under these circumstances gains averaging just 0.5-1.2kg could not be considered undesirable when alternative insulins would be associated with even greater weight gain.

Therefore, Novo Nordisk stated that it (and the licensing authorities) considered that the claim of 'no undesirable weight gain' was substantiated from an up-to-date evaluation of all of the evidence, and that it reflected clearly the available evidence. With regard to all available weight data from the published phase 3 studies, the consistency of the advantage was remarkable. There was a statistically significant relative reduction in final weight (versus comparator) in every study where the parameter had been measured.

Novo Nordisk submitted that further substantiation for a claim of no undesirable weight gain could be found in a meta-analysis of data from all type 2 studies. When patients were stratified by baseline BMI it could be seen that NPH treatment resulted in weight gain in all categories. In contrast, the most weight gain with Levemir occurred in patients in the lowest categories of BMI, with weight loss seen in those with a BMI of 30-35. Above this category, observations became few and unreliable, but the mean level of weight gain with Levemir was negligible. Given that weight gain could be considered desirable when patients were underweight, but undesirable when patients were overweight, the claim was further validated.

COMMENTS FROM AVENTIS

Aventis stated that the basis of its original complaint was that there was insufficient data regarding the use of Levemir in type 2 diabetes to justify the broad claims made for it. This view was upheld by the Panel which considered that the SPC for Levemir did not support any of the four broad claims: a more predictable profile than glargine and NPH; fewer nocturnal hypoglycaemic events than NPH; more effective glycaemic control than NPH and no undesirable weight gain.

Aventis continued to take this view. Moreover in attempting to go beyond the SPC, Novo Nordisk provided additional data from studies of Levemir in type 2 diabetes. However, Aventis alleged that some of the results presented were contradictory.

Aventis noted that Novo Nordisk referenced studies by Raslova *et al* (2004) and Haak *et al* (2005). This information was made publicly available in November 2004 and January 2005, respectively. As neither studies were made available at the time of Aventis' original request (2 August 2004) to Novo Nordisk it was uncertain whether this data was available and thus able to substantiate the claim at the time of preparation of the mailer (May 2004).

With regard to the extrapolation of data from type 1 and type 2 diabetes, Aventis noted that Novo Nordisk had hypothesised that 'many between-treatment differences in the 'behaviour' of an insulin in type 1 diabetes … were also likely to apply in type 2

diabetes, *if* (emphasis added) these arose from inherent pharmacokinetic properties of the insulins tested'.

Aventis noted that its concern with this hypothesis was the conditional requirement – the hypothesis was true, if many between-treatment differences in the 'behaviour' arose only from pharmacokinetic properties. However, it was well-established that 'behaviour' or clinical effect of a medicine depended on both pharmacokinetics (what the body did to the medicine) and pharmacodynamics (what the medicine did to the body). In discussing the clinical effect of a medicine, the two properties could not be separated. In other words, if pharmacodynamics of a medicine were different in type 1 and type 2 diabetes, then extrapolation of data was not valid.

Aventis stated that type 1 and type 2 diabetes were different diseases and pharmacodynamics were different. For example, it was well established that type 2 diabetics were relatively insulin-insensitive compared to type 1 diabetics or those without diabetes. Therefore, this changed the pharmacodynamics, meaning that larger doses were required for type 2 diabetics.

Aventis noted that the Levemir SPC also stated administration once or twice daily depending on patients' needs. This was another degree of variability, which made it difficult to extrapolate data from type 1 and type 2 diabetes.

Aventis continued to believe that type 1 and type 2 diabetes had sufficiently different characteristics such that evidence for the efficacy of any insulin was required in both disease states before broad promotional claims could be made to encompass 'the whole of diabetes'.

A more predictable profile than glargine and NPH

Aventis noted that Novo Nordisk had appealed on the basis of the hypothesis that data from type 1 diabetes could be extrapolated to type 2 diabetes. Novo Nordisk then provided type 2 data of Levemir against NPH as proof of this hypothesis. However, there was no data on Lantus versus Levemir in type 2 diabetes and for this, the appeal was based solely on an extrapolation from a single glucose-clamp study in type 1 diabetes.

Aventis stated that for these reasons it supported the Panel's view that the current data from the type 1 diabetes study was insufficient to support this claim against Lantus. Aventis also agreed with the Panel's view that although there was a statement in Section 5.1 of the SPC stating less variability for Levemir compared to NPH, there was no comparable statement comparing Lantus and Levemir.

Fewer nocturnal hypoglycaemic events than NPH

Aventis noted that in its complaint it could not find evidence for this claim in type 2 diabetes. Novo Nordisk then provided new information – Hermansen (2004(b)) and Raslova. However, the Panel considered that despite this, there was still insufficient information to substantiate this claim in type 2 patients, as only one study (Hermansen 2004(b)) provided a statistically significant finding in favour of Levemir.

Aventis noted that in the appeal there was the addition of a third type 2 diabetes study: Haak (2005). There were now two studies out of three that did not show significant improvements in hypoglycaemia for Levemir against NPH. Novo Nordisk also referred to a meta-analysis, but close inspection of the abstract showed that for the most serious category of hypoglycaemia, major hypoglycaemia, there was no difference.

Aventis noted that the Panel's ruling was that while Section 5.1 of the Levemir SPC stated a lower risk of nocturnal hypoglycaemia against NPH in type 1 diabetes, 'no difference was seen in type 2 diabetes'. The inclusion of data outside of the SPC did not prove otherwise.

More effective glycaemic control than NPH

Aventis noted that in deconstructing the claim, Novo Nordisk discussed two parts: 'effective' and 'glycaemic'. As the Panel had concluded, most clinicians interpreted 'glycaemic control' as referred to HbA_{1c} control as implied in the Levemir SPC, but Novo Nordisk disputed this stating that other parameters were also part of its interpretation.

Aventis firstly, examined the HbA_{1c} data. Novo Nordisk provided data from three studies in type 2 patients. All three results for HbA_{1c} showed that the 95% confidence interval was not statistically significant.

Secondly, Novo Nordisk referred to the use of the word 'effective' together with the word 'glycaemic' to imply that clinicians would interpret the combined phrase 'effective glycaemic control' in the wider context to include fasting blood glucose (FBG) and hypoglycaemia. If a clinician took a position of interpreting 'effective glycaemic control' to include FBG or nocturnal hypoglycaemia, then examination of the type 2 studies showed that these results were also not statistically significant.

Aventis alleged that there were no significant differences between NPH and Levemir in type 2 patients for HbA_{1c}, FBG and major nocturnal hypoglycaemia and thus it considered that the claim could not be substantiated. Furthermore, the data submitted by Novo Nordisk did not change the conclusions in Section 5.1 of the Levemir SPC. This section stated that there were FBG improvements with Levemir compared to NPH for type 1 diabetes, but there was not a comparable statement for type 2 diabetes.

No undesirable weight gain

Aventis noted that firstly, Novo Nordisk claimed that the phrase 'undesirable weight gain' had been used twice in the SPC. Aventis could only find the word 'weight' in two instances:

'In long-term treatment trials, fasting plasma glucose in patients with Type 1 diabetes was improved with Levemir compared with NPH insulin when given as basal/bolus therapy. Glycaemic control (HbA_{1c}) with Levemir is comparable to NPH insulin, with a lower

risk of nocturnal hypoglycaemia and no associated weight gain'.

'Unlike other insulins, intensive therapy with Levemir is not associated with undesirable weight gain'.

Aventis noted that the phrase 'undesirable weight gain' was used in the context of intensive therapy. Intensive therapy was interpreted as a basal-bolus regimen – ie a basal insulin plus mealtime insulins. Novo Nordisk stated that the second statement could be applied in general to type 1 and 2 diabetes. However, intensive therapy was used in a minority of type 2 patients. Thus claiming that there is no 'undesirable weight gain' in all type 2 diabetes was an inaccurate statement according to the actual statement in the Levemir SPC.

Secondly, Novo Nordisk also focussed on the interpretation of the word 'undesirable'. In each of the three type 2 diabetes studies, there was a consistent effect of weight gain (all statistically significant). Aventis alleged that any weight gain in type 2 patients who were typically obese, was undesirable. Although Aventis agreed that less weight gain relative to NPH was desirable, any weight gain *per se* was still undesirable. This was due to the relationship between increasing weight and the decreasing sensitivity to insulin that results.

Thirdly, Novo Nordisk argued that the discrepancy in direction of effect of weight change in type 1 versus type 2 diabetes, might be due to intensification of insulin treatment. Aventis alleged, however, without proof of longer-term studies to show that Levemir also produced no weight gain in type 2 diabetes, it could not see how Novo Nordisk could be certain of this.

APPEAL BOARD RULING

The Appeal Board noted from the Novo Nordisk representatives at the meeting that although the preparation date of the mailing was May 2004, it had not been used until the Levemir launch date, 21 June 2004.

The Appeal Board noted that Haak *et al* and Raslova *et al* had each been published in abstract format prior to May 2004 and had formed part of the regulatory submission for Levemir in February 2004. The Appeal Board noted that whilst the Hermansen *et al* (2004b) data was published as a poster in Europe on 7 September 2004, the data, according to the Novo Nordisk representatives, had been publicly available since 6 June 2004.

A more predictable profile than glargine and NPH

The Appeal Board noted that Section 5.1 of the Levemir SPC stated that the time-action profile of insulin detemir was statistically significantly less variable than for NPH insulin as seen from the within-subject coefficients of variation for the total and maximum pharmacodynamic effect. There was no comparable statement in the SPC with regard to insulin glargine.

The Appeal Board noted the data submitted to substantiate the statement in relation to NPH in type 1 and 2 diabetics. The Appeal Board noted that Heise *et al* compared the within-subject variability of the glucose lowering effect of insulin detemir and insulin glargine in 51 type 1 diabetics each undergoing four clamp procedures. The results suggested that insulin detemir had a significantly more predictable glucose-lowering effect than both NPH insulin and insulin glargine ($p<0.001$). The Appeal Board noted Novo Nordisk's submission that Heise *et al* examined the properties of insulin and not the type of diabetes. Further that the study was the largest clamp study known and that the pharmacodynamic profile of exogenous insulin was more readily demonstrated in type 1 diabetics. The Appeal Board considered that the Heise study was a validated methodology broadly applicable to both type 1 and type 2 diabetics. The Appeal Board noted Heise *et al* and the statement in the Levemir SPC and considered that the claim at issue was capable of substantiation and not inaccurate or exaggerated as alleged. The Appeal Board ruled no breaches of Clauses 7.2, 7.4 and 7.10 of the Code. The appeal on this point was successful.

Fewer nocturnal hypoglycaemic events than NPH

The Appeal Board noted that Section 5.1 of the Levemir SPC stated, with regard to type 1 diabetes, that there was a lower risk of nocturnal hypoglycaemia with Levemir than with NPH insulin. It was further stated that analyses of nocturnal hypoglycaemia in type 1 diabetes showed a significantly lower risk of minor nocturnal hypoglycaemia than with NPH insulin, whereas no difference was seen with type 2 diabetes.

The Appeal Board noted that Novo Nordisk had submitted a number of papers to support the statement in the SPC with regard to type 1 diabetics (Hermansen *et al* 2004a; Home *et al* and Vague *et al*). Three papers had been submitted which dealt solely with the treatment of type 2 diabetics (Hermansen *et al* 2004b, Raslova *et al* and Haak *et al*). Of the three studies only Hermansen *et al* (2004b) with an aggressive treat-to-target protocol had reported a reduced risk (55%) of nocturnal hypoglycaemia in patients treated with insulin detemir (n=71) compared with NPH-treated patients (n=112) that was statistically significant ($p<0.001$).

On balance the Appeal Board thus considered that there was insufficient data to claim that all diabetics treated with insulin detemir would have fewer nocturnal hypoglycaemic events than if they had been treated with NPH. There was data to show that this was the case in type 1 diabetics but insufficient in type 2. The Appeal Board noted the SPC statement in this regard. The Appeal Board thus considered that the claim was inaccurate, misleading and exaggerated as alleged, and upheld the Panel's ruling of breaches of Clauses 7.2, 7.4 and 7.10. The appeal on this point was unsuccessful.

More effective glycaemic control than NPH

The Appeal Board noted that Section 5.1 of the Levemir SPC stated 'In long-term treatment trials, fasting plasma glucose in patients with type 1 diabetes was improved with Levemir compared with NPH insulin when given as basal/bolus therapy.

Glycaemic control (HbA_{1c}) with Levemir is comparable to NPH insulin, with a lower risk of nocturnal hypoglycaemia and no associated weight gain'. The Appeal Board thus considered that, in the context in which it appeared, the statement about glycaemic control related only to type 1 diabetics.

The Appeal Board noted that glycaemic control could be seen as a composite of hypoglycaemic events, HbA_{1c} and weight gain. Given that two of these parameters were already the subject of separate claims it was not unreasonable to assume that 'glycaemic control' in the claim now at issue related only to HbA_{1c}. The SPC stated that, in type 1 diabetics, glycaemic control with Levemir was comparable to NPH insulin and the majority of the papers submitted by Novo Nordisk supported this statement. The Appeal Board considered the balance of evidence was thus that the two insulins were comparable in type 1 diabetics.

With regard to type 2 diabetes, three studies, Hermansen *et al* (2004b), Raslova *et al* and Haak *et al* had compared insulin detemir and NPH insulin in this group. All three studies reported that, in terms of HbA_{1c}, the two insulins were comparable.

The Appeal Board thus considered that, the claim 'more effective glycaemic control than NPH' was inaccurate, misleading and exaggerated as alleged and upheld the Panel's rulings of breaches of Clauses 7.2, 7.4 and 7.10. The appeal on this point was unsuccessful.

No undesirable weight gain

The Appeal Board noted that Section 5.1 of the Levemir SPC stated 'In long-term treatment trials, fasting plasma glucose in patients with type 1 diabetes was improved with Levemir compared with NPH insulin when given as basal/bolus therapy. Glycaemic control (HbA_{1c}) with Levemir is comparable to NPH insulin, with a lower risk of nocturnal hypoglycaemia and no associated weight gain'. In the Appeal Board's view the statement about no associated weight gain referred only to type 1 diabetics. A later statement in Section 5.1 read 'Unlike other insulins, intensive therapy with Levemir is not associated with undesirable weight gain'.

The Appeal Board considered that the SPC wording '**intensive** (emphasis added) therapy with Levemir is not associated with undesirable weight gain' was not the same as the claim at issue 'No undesirable weight gain'; the SPC wording was clearly linked to an intensive dosing regimen.

The Appeal Board noted there was data indicating a small weight loss (Hermansen *et al* 2004(a), Russell-Jones *et al* 2004(a), Standl *et al* and Vague *et al*), or no weight loss (Home *et al*) in type 1 diabetics treated with a non-intensive Levemir dosing regimen. Conversely, type 2 diabetics treated with a non-intensive regimen reported a weight increase; Haak *et al*, Hermansen *et al* 2004(b) and Raslova *et al*.

The Appeal Board noted that 'undesirable' had not been defined in terms of weight gain, any weight gain might or might not be undesirable depending upon the patient.

The Appeal Board considered that the claim at issue 'no undesirable weight gain' implied that no diabetic patient, type 1 or type 2, would gain weight with Levemir and this was not so. No data had been submitted to show no weight gain in type 2 diabetics on a non-intensive dosing regimen of Levemir. The claim was thus inaccurate, unsubstantiated and exaggerated as alleged. The Appeal Board upheld the Panel's ruling of breaches of Clauses 7.2, 7.4 and 7.10 of the Code. The appeal on this point was unsuccessful.

2 Claim 'Levemir FlexPen (insulin detemir) predictable results day after day'

This claim appeared as a strapline beneath the product logo on pages 1, 3 and 4.

COMPLAINT

Aventis stated that in order to substantiate this claim, Novo Nordisk must be able to provide data showing 'predictability' for Levemir in type 1 and type 2 diabetics. Novo Nordisk had not provided Aventis with such data. It therefore alleged that this claim for Levemir FlexPen was inaccurate, unsubstantiated and exaggerated, in breach of Clauses 7.2, 7.4 and 7.10.

RESPONSE

Novo Nordisk stated that this had already been discussed in detail above. The Levemir SPC stated 'the time action profile for insulin detemir is statistically significantly less variable than for NPH…'. Less variability implied predictable results, a point also made by Aventis in Case AUTH/1593/6/04. This claim was supported by corroborative evidence published in papers by Heise *et al*, Russell-Jones *et al*, Home *et al*, Hermansen *et al*, Haak *et al* and Raslova *et al*. These included data on both type 1 and type 2 diabetes.

PANEL RULING

The Panel noted that the relevant claim considered in point 1 above, 'a more predictable profile than glargine and NPH', was a comparative claim. The claim now at issue was not – it was an absolute claim that Levemir FlexPen produced predictable results day after day.

The Panel noted that Section 5.1 of the Levemir SPC stated that 'The time action profile of insulin detemir is statistically less variable than for NPH insulin as seen from the within-subject coefficients of variation (CV) for the total and maximum pharmacodynamic effect'. The CVs for Levemir were 27% and 23% respectively. The SPC referred to a 'more reproducible absorption and action profile of insulin detemir compared to NPH insulin'. It was also stated that 'Lower day-to-day variability in FPG was demonstrated during treatment with Levemir compared to NPH in long-term clinical trials'. There was no statement that Levemir was predicable *per se*.

With regard to published data in type 1 diabetics, it had been demonstrated that although there was less

within-person variability with Levemir than with NPH insulin (Hermansen *et al* 2004a; Home *et al*; Russell-Jones *et al* 2004a and Vague *et al*) there was, nonetheless, some variability. Haak *et al* and Raslova *et al* reported similar results in patients with type 2 diabetes.

The Panel considered that whilst the concept of predictability of response to insulin was understood by health professionals the claim at issue 'predictable results day after day' implied that there would be no within-person variation in glycaemic control with Levemir, which was not so. The claim was a strong, absolute claim which was not supported by the data. The Panel thus considered that the claim was misleading, unsubstantiated and exaggerated as alleged; breaches of Clauses 7.2, 7.4 and 7.10 were ruled.

APPEAL BY NOVO NORDISK

Novo Nordisk submitted that the word 'predictable' in the claim 'predictable results day after day' would not be construed as an absolute, as argued by Aventis and ruled by the Panel.

Novo Nordisk submitted that 'predictable' was not an absolute word. To the clinician 'predictable' meant something that could be expected within reason. For instance, if a clinician obtained two consecutive low blood pressure readings for a patient (s)he would probably predict that the next measurement would also be low and that it would not be high when repeated in 6 months. If this expectation was borne out, the clinician would regard that patient's blood pressure as 'predictable', whereas a patient that produced inconsistent readings varying between hypertensive and normal values would be regarded as having an 'unpredictable' blood pressure. Similarly, for blood glucose level, serial measurements of 5.5, 5.4 and 5.6mmol/l would be construed as showing predictability. To require a reading of blood pressure or blood glucose with absolute repeatability from one day to the next was defying human physiology. In support of this concept, Novo Nordisk noted that the Cambridge online dictionary defined 'predictable' as: '... if something is predictable, you know in advance that it will happen or what it will be like'. The Online Compact Oxford English dictionary gave the definition: '… always behaving or occurring in the way expected'.

Novo Nordisk submitted that neither definition could be considered as an 'absolute'. The Cambridge dictionary's use of the phrase '…what it will be like' implied an approximation to an expectation, while the Oxford dictionary's phrase '… the way expected' reiterated its reasoning that the audience's expectations for an insulin would not be for unwavering results, but rather for results that would routinely approximate to their mean value.

Novo Nordisk submitted that the issue of expectation was key here. Marketing terms needed to be set in the context of the target audience's experience. Car drivers perceived a 'reliable' car as one that normally did not break down, although it could do on rare occasions. Similarly, for a diabetes specialist prescribing insulin, 'predictable results' meant that measured values from serial measurements would tend to cluster closely, although again deviations might occur on rare occasions, such as when patients went out and had a heavy drink, or had a concurrent illness. Here, of course, the insulin might still be performing in a predictable way in terms of its time-action profile, but the patient's behaviour had introduced a variable. Diabetes specialists were well aware of such possibilities and of the expectations they could place on their patients and the insulins prescribed.

Novo Nordisk submitted that there needed to be some room in the choice of marketing terminology, as long as the terminology conveyed what clinicians could reasonably expect. In this case, no clinician reading the strapline 'predictable results' would assume that a blood glucose level of 5.5mmol/l would repeat itself with absolute precision indefinitely; much as a car driver who drove a reliable car did not expect the car to never break down.

Novo Nordisk submitted that the word 'results', was a general term. To the diabetes specialist audience 'results' implied blood glucose levels and the risk of hypoglycaemia. More generally, it also implied the overall health outcome of the patient receiving the medicine. Taken together, 'predictable results' meant blood glucose levels with similar but not identical blood glucose levels, and a low risk of hypoglycaemia associated with this blood glucose level. Meanwhile, 'day after day' was simply a phrase to complement the word 'predictable'. The English language lent itself to phrases and words to complement one another. Without 'day after day', the phrase 'predictable results' still conveyed much the same meaning. A parallel would be 'a reliable car that seldom breaks down', where 'seldom breaks down' complemented 'reliable'.

COMMENTS FROM AVENTIS

Aventis noted that Novo Nordisk claimed that the word 'predictable' used in this context did not imply an absolute quality, but a sense of reasonable expectation. However, the Panel disagreed with this line of reasoning and noted that there was indeed some variability.

Aventis drew attention to the Levemir SPC, which stated that Levemir should be administered once or twice daily depending on patients' needs. Aventis alleged that at initiation of therapy, health professionals could not reasonably predict who would require once or twice daily administration of Levemir. Thus, even when this claim was interpreted in the manner Novo Nordisk suggested, it still could not see how Levemir could be reasonably predictable.

Aventis considered that it was essential that all promotion must be done in a responsible and professional manner, particularly in regard to claims made within the SPC, and so it continued to object to these claims. Aventis alleged that it was clear from its evaluation that the Levemir SPC could not substantiate these broad claims. Furthermore, Aventis' review of data outwith the SPC provided by Novo Nordisk in its appeal did not support these claims. Thus Aventis continued to support the Panel's ruling.

APPEAL BOARD RULING

The Appeal Board noted that Section 5.1 of the Levemir SPC stated that 'The time action profile of insulin detemir is statistically less variable than for NPH insulin as seen from the within-subject coefficients of variation (CV) for the total and maximum pharmacodynamic effect'. The CVs for Levemir were 27% and 23% respectively and for NPH insulin the figures were 68% and 46%. The SPC referred to a 'more reproducible absorption and action profile of insulin detemir compared to NPH insulin'. It was also stated that 'Lower day-to-day variability in FPG was demonstrated during treatment with Levemir compared to NPH in long-term clinical trials'.

With regard to published data in type 1 diabetics, it had been demonstrated that there was less within-person variability with Levemir than with NPH insulin (Hermansen *et al* 2004a; Home *et al*; Russell-Jones *et al* 2004a and Vague *et al*). Haak *et al* and Raslova *et al* reported similar results in type 2 diabetics.

The Appeal Board considered that the concept of predictability of response to insulin was understood by health professionals and thus the claim at issue 'predictable results day after day' (emphasis added) would not be interpreted as a claim of absolute predictability. Although the claim was a strong claim, it was substantiable both by the SPC and by published data. The Appeal Board thus considered that the claim was not misleading or exaggerated as alleged; no breaches of Clauses 7.2, 7.4 and 7.10 were ruled. The appeal on this point was successful.

3 Use in children and adolescents

COMPLAINT

Aventis stated that the use of the broad claims highlighted above in points 1 and 2, not only implied that the claims related to the use of Levemir across type 1 and type 2 diabetes, but also suggested that this insulin would be appropriate for use in children and adolescents, who were recognised as an important and distinct subgroup of diabetics. The SPC for Levemir stated 'The efficacy and safety of Levemir have not been studied in children and adolescents'. Aventis alleged that the claims were therefore both outside the terms of the marketing authorization and inconsistent with the Levemir SPC in breach of Clause 3.2.

RESPONSE

Novo Nordisk stated that it was not its intention to suggest that Levemir would be appropriate for use in children and adolescents. The prescribing information clearly stated that there were 'no studies in children and adolescents'. A new study with Levemir in children had now been completed and published.

It was neither common practice nor practicable to list the warnings for all the subgroups of diabetics in a strapline on the front page of a promotional piece, as clearly there were a large number of subgroups with many permutations. For instance, subgroups using insulin included pregnant or lactating women, patients with hypo-albuminaemia and patients who drove (and might therefore suffer hypoglycaemia a known side effect of any insulin). These were all duly listed in the prescribing information.

Straplines were by nature succinct and not exhaustive. The indications, contra-indications, and precautions were all clearly listed in the prescribing information to enable the prescriber to check. This practice was common with all pharmaceutical companies.

PANEL RULING

The Panel noted that Section 4.2 of the Levemir SPC stated that the efficacy and safety of Levemir had not been studied in children and adolescents. Section 5.2 explained that the pharmacokinetics of Levemir were investigated in children (6-12 years) and adolescents (13-17 years) and compared to adults with type 1 diabetes. There was no clinically relevant difference in pharmacokinetic properties. As the pharmacokinetics had not been studied extensively in these populations it was advised to monitor plasma glucose closely in these populations. The Panel noted that the use of Levemir was not contraindicated in children.

The Panel noted that neither the front cover nor inside pages of the mailing referred to the use of Levemir in children or adolescents. The graphics did not show a child or adolescent. In the context in which they were made, the Panel thus did not consider that the claims at issue at points 1 and 2 were inconsistent with the marketing authorization on this point as alleged. No breach of Clause 3.2 was ruled.

4 Claim '… in a reliable pen'

COMPLAINT

Aventis was unsure of the exact meaning of the unreferenced claim '…in a reliable pen'. If 'reliable' was used as an absolute term then it suggested to health professionals that the Levemir FlexPen was 100% reliable. In order to be substantiable, Novo Nordisk would have to provide the data that no FlexPen malfunctions or failures had ever been recorded. Moreover, as this mailing was used to promote the launch of the UK product the data could not refer to the Levemir FlexPen, but presumably to clinical experience of other FlexPen insulin presentations (NovoMix 30 and NovoRapid) that were available in UK. It seemed highly unlikely that Novo Nordisk could produce such data so the claim was likely to be inaccurate, unsubstantiable and exaggerated, in breach of Clauses 7.2, 7.4, 7.10. Alternatively, if 'reliable' was used as a relative term then it suggested to health professionals that Levemir FlexPen was more reliable than an unspecified comparator device. If this was the intention, the claim was at best a hanging comparison in breach of Clause 7.2.

Aventis had asked Novo Nordisk to explain what the claim '…in a reliable pen' meant and it had not replied. Aventis alleged that the claim was ambiguous in breach of Clause 7.3, and in addition,

depending on the intended impression, in breach of the clauses listed above.

RESPONSE

Novo Nordisk explained that FlexPen was a pre-filled injection device used for Novo Nordisk insulins such as Levemir, NovoRapid, and NovoMix 30.

Reliability, as defined by the Dictionary of Science and Technology, meant: 1 *in engineering*: the probability that a product would be operational after a period of usage or over a specified time period, based on testing of the product under a prescribed operation and operating environment; 2 *in statistics*: the analysis of the life distribution of systems subject to random failures; or the probability that a system would accomplish a given task.

Novo Nordisk stated that it used the claim 'reliable pen' to describe the FlexPen as a delivery system with a good accuracy, safety record and low failure rate. The FlexPen had been developed in compliance with ISO 11608-1, a standard set by the International Organization for Standardization which set out the accuracy requirements, test methods and failure rates for pen injectors for medical use. ISO 11608-1 was intended to 'verify, at a high confidence level, the manufacturer's ability to manufacture one 'lot' of pen-injectors that conforms to the critical product attributes'. Novo Nordisk pointed out that international standards emphasized 'high confidence level', and not 'absolute' level which would be an impractical demand on manufacturing. This standard accepted a small error rate in dose accuracy. Aventis' assertion that Novo Nordisk had to prove 'absolute' 100% reliability ran contrary to established international standards.

With compliance to the ISO 11608-1, Novo Nordisk had ensured that each FlexPen has passed European Standard statistical and quality tests in order to be deemed reliable for human use.

The reliability of FlexPen was supported by the Novo Nordisk Quality System which continuously monitored market feedback. FlexPen had, since launch in 2001, had a very low complaint rate.

Confidential data from Novo Nordisk indicated that globally the failure rate of the FlexPen was less than one in 50,000.

In the 12-month period from Q3 2003 to Q2 2004, the number of verified faults related to FlexPen was 23 in the UK, set against total sales of 522,817 units (each unit contained 5 FlexPens) or a total of 2,614,085 sold. This was equivalent to 0.00088%, or just under 9 out of 1,000,000.

Furthermore, by saying '…. in a *reliable* pen' (emphasis added) in a separate statement detached from the four bullet points which were specific to the properties of the insulin (ie Levemir), Novo Nordisk had separated the properties of FlexPen from the properties of Levemir. Hence the properties of FlexPen needed to be considered independently from the properties of Levemir, and the word 'reliable' referred to FlexPens in general and not *just* FlexPen that contained Levemir.

Novo Nordisk disagreed with Aventis' submission that the word 'reliable' must either be absolute or relative. The use of the word 'reliable' was neither. 'Reliable' was not absolute as it carried 'probability' in both engineering and statistics, as defined above. 'Reliable' indicated a low probability of failure. Grammatically Novo Nordisk had not used the comparative phrase 'more than', hence it had not mentioned a comparator device. The word 'reliable' was used as an accurate descriptive term for a device with a sound record, used by millions of diabetics across the world.

PANEL RULING

The Panel noted Novo Nordisk's submission that '… in a reliable pen' referred to FlexPen as a delivery system in relation to its accuracy, safety and failure rate. The Panel considered that readers would assume that the claim at issue referred to the delivery system ie the pen. Data relating to the use of the pen with other insulins would thus be relevant. The Panel did not consider that the claim suggested that Levemir FlexPen was 100% reliable as alleged by Aventis, ie that no malfunctions or failures had ever been recorded. The Panel did not consider the claim to be misleading, incapable of substantiation or exaggerated as alleged; no breach of Clauses 7.2, 7.4 and 7.10 was ruled.

The Panel did not consider that the phrase was directly or indirectly comparative; it was not a hanging comparison as alleged; no breach of Clause 7.2 was ruled.

The Panel noted that Aventis had also alleged that the claim was ambiguous in breach of Clause 7.3 which referred to comparative claims. The Panel noted its comments and rulings above. The Panel did not consider the claim comparative. No breach of Clause 7.3 was ruled.

5 Failure to substantiate claims

COMPLAINT

Aventis stated that it wrote to Novo Nordisk on 2 August expressing its concerns. Novo Nordisk replied in 16 August stating that the mailing in question was being withdrawn from circulation. Aventis considered this response to be unsatisfactory for two reasons. Firstly, Aventis had asked for data to substantiate a number of claims but Novo Nordisk had failed to provide it in breach of Clause 7.5. Secondly, Novo Nordisk continued to use the same or very similar claims for Levemir in a number of other promotional items.

RESPONSE

Novo Nordisk stated that it replied to Aventis' letter on 16 August informing Aventis that it was in the process of revising its promotional materials, and would withdraw the material Aventis challenged. Novo Nordisk noted that Aventis wrote to the Authority on the same day, 16 August, to lodge a further complaint about the mailing.

Aventis demanded in its letter dated 2 August that Novo Nordisk withdraw the material above, and alleged in the letter to the Authority that Novo Nordisk was in breach of Clause 7.5 by not providing Aventis with substantiation.

Novo Nordisk disputed this. The four bullet points on the front page of the mailing were substantiated by published references and hence Novo Nordisk did not reproduce these for Aventis. Aventis did not specifically challenge a diagram on page 3 which was supported by 'data on file' and did not request this reference. Therefore Novo Nordisk did not send the data to Aventis. Novo Nordisk considered that, as the mailing was being withdrawn, it did not need to send duplicate copies of the published references to Aventis.

PANEL RULING

The Panel noted that Aventis had requested substantiation of claims. Novo Nordisk stated that as the bullet points at issue at point 1 above were substantiated by the cited references which were published and publicly available it did not reproduce these for Aventis. Further the item was being withdrawn. The Panel considered that these reasons were inadequate; substantiation had to be provided irrespective of whether the references were publicly available or whether the item was to be withdrawn. A breach of Clause 7.5 was ruled.

Complaint received **18 August 2004**

Case completed **29 March 2005**

CASE AUTH/1628/9/04

AVENTIS PHARMA v NOVO NORDISK

Levemir launch pack

Aventis Pharma complained about a launch pack for Levemir (insulin detemir) which had been delivered to health professionals by Novo Nordisk. The pack comprised of a large cardboard box which featured promotional claims for Levemir FlexPen and contained *inter alia* two rulers and a cookbook 'Healthy Eating for Diabetes'.

The rulers had a 24cm scale and featured the Levemir FlexPen logo centred in the middle of a green block curve, the outline of which, in the opinion of Aventis closely resembled the Levemir time-action profile depicted on other promotional items. The use of the time-action profile was a product claim; it suggested the profile of activity that health professionals could expect over 24 hours of Levemir. Aventis was sure that the 24cm scale was a surrogate for 24 hours. Aventis alleged that the rulers constituted disguised promotion, which together with the omission of prescribing information was a breach of the Code. Furthermore, it was unclear whether the representation of the time-action profile represented that to be expected following once or twice daily administration of Levemir. Aventis suggested that given the dosing instructions listed in the Levemir summary of product characteristics (SPC) that the insulin 'should be administered once or twice daily depending on patients' needs, no single unqualified schematic representation could ever be anything other than misleading. Aventis alleged that this unqualified representation of the time-action profile for Levemir was thus in breach of the Code.

The Panel noted Novo Nordisk's submission that the green block curve was simply a representation of Levemir as a basal insulin. The Panel noted that the profile of the curve was almost identical to a graph used by Novo Nordisk in other material to depict the time-action characteristic of Levemir.

The Panel noted that recipients of the launch box would not necessarily be aware that the unlabelled green curve reflected the time-action characteristics of Levemir; it did not appear elsewhere on or within the launch pack. On balance the Panel thus considered that given the context in which the rulers were provided the green block curve did not constitute a product claim as alleged. The inclusion of the rulers in the launch pack meant that in this context the rulers met the requirements for the labelling of promotional aids and no breach of the Code was ruled. The rulers were clearly promotional items for Levemir FlexPen and were not disguised in this regard; no breach of the Code was ruled.

The Panel noted its ruling above and considered that in this context as the green block curve did not constitute a product claim it thus followed that the curve was not misleading in this regard. No breach of the Code was ruled.

Aventis noted that the cookbook, 'Healthy Eating for Diabetes' was provided with a promotional wraparound and a sticker on the back cover which read 'This cookbook is supported by an educational grant from Novo Nordisk to mark the launch of Levemir (insulin determir)'.

Aventis stated that Novo Nordisk had explained that the cookbook was a promotional item, intended for health professionals to distribute to diabetics as part of their education to help them improve their diets. Aventis found it difficult to understand how the provision of a single copy of the book would allow that. However, if this was the case, the sticker on the back cover together with the wraparound sleeve constituted an advertisement for Levemir to the general public.

The Panel noted that the cookbook was an integral part of the launch pack. The loose wraparound sleeve bore a similar promotional theme to the cardboard box and read "'Healthy Eating for Diabetes" is supported by an educational grant from

Novo Nordisk to mark the launch on 21st June 2004 of Levemir FlexPen'. A similar declaration appeared on the sticker on the back cover. The book included a foreword by a diabetes charity, discussed the management of diabetes together with suitable recipes.

The Panel noted Novo Nordisk's submission that health professionals might use the cookbook to educate diabetics about healthy living. Whilst diabetics might find the book helpful the Panel considered that providing a single copy within the context of the Levemir launch pack meant that it was likely to be used personally by the recipient. There were no instructions about the book's intended use nor was it designed with tear-off pages or suchlike that could readily be provided to patients.

The Panel considered that health professionals would consider the cookbook was a personal gift. The provision of only one copy added to that impression. In the Panel's view health professionals would be unlikely to give the cookbook to patients. Nevertheless Novo Nordisk submitted that this was a possibility. The inside front cover clearly referred to 'managing your diabetes' implying that the book was for diabetics. In the Panel's view supplying the cookbook with the sticker to the public meant that Novo Nordisk was promoting a prescription only medicine to the public. A breach of the Code was ruled.

Upon appeal by Novo Nordisk, the Appeal Board was concerned that the company had provided conflicting explanations about the intended use of the cookbook. Intercompany correspondence referred to its distribution to diabetics as part of an educational package. At the appeal hearing the company representatives explained that this was incorrect and that the book was for use with patients but was not meant to be given to them. There was no representatives' briefing material or instructions to health professionals explaining the purpose of the book. The Appeal Board noted the company's written submissions and considered that the position was unclear.

The Appeal Board considered that, whatever the intended purpose of the cookbook, there was a possibility that it would be given to a patient. In such circumstances the sticker on the back would be regarded as an advertisement for a prescription only medicine to the general public. The Appeal Board upheld the Panel's ruling of a breach of the Code.

Aventis stated that the claims 'The future is predictable' which appeared on the inside cover of the launch box and 'Predictable. A new basal analogue' which appeared on the wraparound sleeve for the cookbook were inadequately supported by the references provided. Aventis alleged that given that at the outset of therapy, neither physician nor patient could be certain whether Levemir would require once or twice daily dosing – this did not constitute predictability.

The Panel considered that the claim would be read within the context of the claims for predictability on the launch pack and the items within, which included the second claim at issue 'Predictable. A new basal analogue.' The box, cookbook wraparound and other items all referred to '...predictable results day after day' which appeared as a strapline as part of the product logo. The Panel did not consider that either claim was misleading or incapable of substantiation merely because the dosing regimen was unknown at initiation of treatment as alleged. No breach of the Code was ruled on this narrow point.

Aventis alleged that, overall, the launch pack, together with its contents was in breach of the Code with regards to the requirements on size of materials, high standards had not been maintained; the items and claims listed above disregarded both the letter and spirit of the Code.

The Panel noted that the launch box was 41.5 x 34 x 4.5cm and was to be delivered by Novo Nordisk employees. Nonetheless the Panel considered that the size of the box was extreme and would cause inconvenience. It thus failed to comply with the Code which required *inter alia* that extremes of format and size must be avoided. A breach of the Code was ruled.

The Panel noted its rulings above but did not consider that the material in its totality failed to maintain high standards; no breach of the Code was ruled.

Aventis Pharma Ltd complained about a launch pack (ref DM/080/0504) for Levemir (insulin detemir) which had been delivered to health professionals by Novo Nordisk Limited to mark the launch of the product. The pack comprised of a large cardboard box which featured promotional claims for Levemir FlexPen. The box contained a laminated promotional card (ref DM/075/0504), a booklet (ref DM/070/0504), a number of branded items (an A4 pad, a post-it note pad, two rulers and a box of peppermint sweets) and a cookbook entitled 'Healthy Eating for Diabetes' with a promotional wraparound (ref DM/067/054).

Correspondence with Novo Nordisk had failed to satisfy all of Aventis' concerns. Aventis supplied Lantus (insulin glargine).

1 Rulers

One of the rulers was supplied in a special slot in the launch pack the other was presented as a bookmark in the cookbook.

COMPLAINT

Aventis stated that the two rulers, of similar design, each had a 24cm scale divided into millimetres and marked and numbered at centimetre intervals together with the Levemir FlexPen logo centred in the middle of a green block curve. The outline of the green shape closely resembled the Levemir time-action profile depicted on other promotional items for Levemir. Aventis considered that the use of the time-action profile in this context was a clear product claim; it suggested the profile of activity that health professionals could expect over 24 hours of Levemir. It was highly unusual to have a ruler of 24cm length (they were usually of 15 or 30cm) and Aventis was

sure that the 24cm scale was no coincidence and was a surrogate for 24 hours. Aventis alleged that the rulers constituted disguised promotion, in breach of Clause 10.1, and the omission of prescribing information was a breach of Clause 4.1.

Furthermore, with regard to the time-action profile schematic itself, the summary of product characteristics (SPC) for Levemir stated that the insulin 'should be administered once or twice daily depending on patients' needs. It was unclear whether this representation of the time-action profile represented that to be expected following once or twice daily administration of Levemir. Aventis suggested that given the dosing instructions listed in the SPC, no single schematic representation, without qualification, could ever be anything other than misleading to a health professional. Aventis therefore alleged that this unqualified representation of the time-action profile for Levemir was misleading in breach of Clause 7.2 and, in the absence of evidence to the contrary, Clause 7.4.

RESPONSE

Novo Nordisk stated that the rulers were not intended to carry an indication of the time-action profile of Levemir. The image was simply a representation of Levemir as a basal insulin. Aventis suggested that the rulers carried a product claim. However, the rulers carried no time scale along the horizontal axis, just the usual markings of millimetres and centimetres and no vertical scale.

No item in the launch box carried any claim about duration of action of 24 hours. On the titration chart included in the box, some recommendations for use of Levemir were given; these were in line with the SPC and no claim for 24 hours was made. The key promotional claim for Levemir was 'predictable results day after day' printed on the front of the box; other important claims included.

Novo Nordisk noted that Aventis, which claimed 24-hour action for Lantus, had tried to second-guess the product claim of another basal insulin, Levemir.

Logos and imageries such as this were frequently used in promotional items to give a brand a recognisable image. Advertisements using different logos or images could be found in many medical journal; examples were provided.

The rulers were promotional aids which fulfilled the criteria set out in Clause 18.3 as there were no promotional claims. Hence no prescribing information was included. The rulers were a one-off give-away during the launch of Levemir and were no longer in circulation.

Novo Nordisk found Aventis' allegations of a breach of Clauses 7.2 and 7.4 baffling: there were no promotional claims on the rulers and these two clauses applied to accuracy of information and substantiation of claims.

PANEL RULING

The Panel noted that each ruler depicted a symmetrical curve, in green block which ran from 1-24cm in the centre of which appeared 'Levemir FlexPen' in logo format.

The Panel noted Novo Nordisk's submission that the green block curve was simply a representation of Levemir as a basal insulin. The Panel noted that the profile of the curve was almost identical to a graph used by Novo Nordisk in other material to depict the time-action characteristic of Levemir. The Panel noted that this time-action characteristic graph did not appear on the promotional box or on the laminated card or in the booklet. The laminated card and booklet however referred to Levemir's predictable profile.

The Panel noted that a promotional aid did not require prescribing information if it included no more than: the name of the medicine, an indication that the name of the medicine was a trademark and the name of the company marketing the product.

The Panel noted that recipients of the launch box would not necessarily be aware that the unlabelled green curve reflected the time-action characteristics of Levemir; it did not appear elsewhere on or within the launch pack. On balance the Panel thus considered that given the context in which the rulers were provided the green block curve did not constitute a product claim as alleged. The inclusion of the rulers in the launch pack meant that in this context the rulers met the requirements for the labelling of promotional aids set out in Clause 18.3 and thus no breach of Clause 4.1 was ruled. The rulers were clearly promotional items for Levemir FlexPen and were not disguised in this regard; no breach of Clause 10.1 was ruled.

The Panel noted its ruling above and considered that in this context that as the green block curve did not constitute a product claim it thus followed that there could be no breach of Clauses 7.2 and 7.4 of the Code; no breach of those clauses was ruled.

2 Cookbook

A cookbook, 'Healthy Eating for Diabetes' was provided with a promotional wraparound and a sticker on the back cover which read 'This cookbook is supported by an educational grant from Novo Nordisk to mark the launch of Levemir (insulin determir)' (ref DM/067/054). The front cover referred to a diabetes charity; the normal retail price of the book, on the inside front cover, was £12.99.

COMPLAINT

Aventis stated that Novo Nordisk had explained that 'the cookbook was a promotional item, intended for health professionals to distribute to diabetes patients as part of their educational package to help them achieve improvements in their dietary habits'. Aventis found it difficult to understand how the provision of a single copy of this book would allow health professionals to distribute it to their patients. However, if this was the case, the sticker on the cover of the book stating 'This cookbook is supported by an educational grant from Novo Nordisk to mark the launch of Levemir' together with the wraparound sleeve claiming 'Predictable. A new basal analogue'

constituted an advertisement for Levemir to the general public, in breach of Clause 20.1.

RESPONSE

Novo Nordisk stated that the cookbook was provided to health professionals who might want to use it to educate diabetics about healthy eating. Weight management played an important role in the management of diabetes. Novo Nordisk submitted that each cookbook had cost less than £6 (plus VAT) as they had been purchased in bulk. Health professionals could distribute them to patients if they so chose, just as they could give away branded post-its and pens. Alternatively, health professionals could go through the ingredients of recipes and their quantities in the cookbook with patients for educational purposes. This was not an uncommon practice amongst dieticians. Novo Nordisk believed as a responsible pharmaceutical company it had provided a very useful tool for health professionals in the management of diabetes.

The wraparound sleeve over the cookbook was loose and detachable. While there was a sticker on the back cover, the cookbooks were given to health professionals, not members of the general public. This give-away was consistent with other common give-aways such as pens and post-its, which of course could also flow into the hands of the public indirectly.

Provision of a cookbook with a loose wraparound sleeve to health professionals did not, in Novo Nordisk's view, constitute advertising to the public and thus was not a breach of Clause 20.1 of the Code.

PANEL RULING

The Panel noted that the cookbook was an integral part of the launch pack. The loose wraparound sleeve bore a similar promotional theme to the cardboard box and read "'Healthy Eating for Diabetes" is supported by an educational grant from Novo Nordisk to mark the launch on 21st June 2004 of Levemir FlexPen.' A similar declaration appeared on the sticker on the back cover. The book included a foreword by a diabetes charity, discussed the management of diabetes and featured a selection of suitable recipes.

The Panel noted Novo Nordisk's submission that health professionals might use the cookbook to educate diabetics about healthy living. Whilst the Panel noted that diabetics might find the book helpful, it considered that providing a single copy to health professionals within the context of a launch pack for Levemir meant that it was likely to be used by the recipient for his or her personal use. There were no instructions to health professionals about the book's intended use nor was it designed with tear-off pages or suchlike that could readily be provided to patients.

The Panel considered that health professionals would consider the cookbook was a gift and part of the launch of Levemir. The provision of only one copy added to the impression that it was for personal use. In the Panel's view health professionals would be unlikely to give the cookbook to patients.

Nevertheless Novo Nordisk submitted that this was a possibility. The inside front cover clearly referred to 'managing your diabetes' implying that the book was for diabetics. In the Panel's view supplying the cookbook with the sticker to the public meant that Novo Nordisk was promoting a prescription only medicine to the public. A breach of Clause 20.1 of the Code was ruled.

During its consideration of this case the Panel was concerned that Novo Nordisk submitted that the cookbook was an acceptable give-away. The Panel disagreed. As noted in the ruling it was unacceptable to give the cookbook to the public because of the sticker. The Panel considered that it was unacceptable to give the cookbook to a health professional without explaining the purpose. The Panel queried whether the cookbook was a promotional aid that met the requirements of the Code. It had not been told of the cost, which had to be £6 or less. VAT was not charged on books. The Panel was also concerned that if the cookbook was intended for health professionals' personal use it did not meet the requirement that promotional aids had to be relevant to the recipient's profession or employment. The Panel did not accept Novo Nordisk's view that the cookbook was the same as pens and post-it notes. It requested that its views be drawn to Novo Nordisk's attention.

APPEAL BY NOVO NORDISK

Novo Nordisk submitted that the cookbook was provided to health professionals who might want to use it to educate diabetics about healthy eating.

In Novo Nordisk's view the cookbook was an important educational tool for diabetics. It was not an ordinary cookbook; it was designed to promote healthy eating to diabetics. The book was supported by a diabetes charity. A foreword written by the charity's executive director explained the importance of healthy eating and stated 'For too many years, people with diabetes have seen their diagnosis as marking the end of enjoyable meals and the beginning of a poorer quality of life … Dispelling the myth that the diabetic diet is dull, while also improving understanding of diabetes and nutrition, Healthy Eating for Diabetes is both education and inspiring…'. In fact, an unhealthy diet could aggravate obesity which in turn worsened insulin resistance and made the control of diabetes more difficult.

The first few pages of the cookbook, written in patient-friendly language, gave useful information and tips such as:

- general information about diabetes
- food – carbohydrate and glycaemic index, fats and protein, fruits and vegetables
- advice on alcohol
- Dose Adjustment For Normal Eating Programme (DAFNE) – an educational programme for people with insulin-treated diabetes
- cooking tips
- eating out (eg what to choose when going out for an Indian meal)

- what to look for when shopping (advice on food labelling)
- weight management

Health professionals, including dieticians, could use the cookbook to go through ingredients in recipes to foster habits of healthy eating among diabetics. One often heard about the unhealthy diet of many diabetics, and how difficult it could be to draw concrete examples of how healthy meals could be prepared with good ingredients and a healthy way of cooking. Providing such a valuable item fulfilled a genuine educational need, and represented an activity all ethical pharmaceutical companies should aspire to. Such initiatives should surely be applauded.

Novo Nordisk noted that the Panel had stated that health professionals might keep the cookbook for their own personal use. Novo Nordisk submitted that any such personal use by health professionals (ie if they used the recipes and cooked themselves) fulfilled the spirits of promoting healthy eating to a wider audience. The company would be delighted to see the recipes put to good use by doctors, nurses and dieticians themselves.

In relation to Clause 20.1 Novo Nordisk stated that whilst there was a sticker with Levemir on the back of the cookbook, the cookbooks were given to health professionals, not members of the general public. Each health professional was given a launch pack containing one cookbook, it was difficult to see how a health professional could select one of their many patients to give the cookbook to. The fact that each health professional was only given a single copy of the cookbook also supported the fact that this was never meant to be an extensive campaign aimed at the general public.

Novo Nordisk submitted that the cookbook, whilst consistent with other common give-aways such as pens and post-its, added more value to the clinical care of diabetics than those give-aways.

Novo Nordisk could not dictate whether a health professional could pass the cookbook on to patients. Even if a cookbook flowed into the hands of the general public, it was not a deliberate attempt to promote to the public. Even Aventis stated that it could not understand how the provision of a single cookbook would allow health professionals to widely distribute to their patients. In other words, Aventis implied that it agreed that this was not a deliberate attempt to promote to the general public.

Finally, the Panel stated that 'the fact that only one copy was provided added to the impression that it was for personal use. In the Panel's view health professionals would be unlikely to give the cookbook to patients'. The Panel's ruling of breach of Clause 20.1 was therefore inconsistent with its stated view on the matter.

Although the cost of the cookbook was not part of a formal complaint, Novo Nordisk confirmed that the cost of each copy was less than £6.

COMMENTS FROM AVENTIS

Aventis submitted that the Panel's ruling was correct. Novo Nordisk continued to be unclear as to whether the single copy of the cookbook, was intended to be used by health professionals as an educational tool with their patients or whether it was a gift for their own personal use. If the former was intended, the sticker on the cover constituted an advertisement for Levemir to the general public as the Panel ruled. If, however, the latter was intended then this promotional aid should comply with Clause 18 of the Code.

APPEAL BOARD RULING

The Appeal Board was concerned that Novo Nordisk had provided conflicting explanations about the intended use of the cookbook. Intercompany correspondence referred to its distribution to diabetic patients as part of an educational package. At the appeal hearing the company representatives explained that this was incorrect and that the book was for use with patients but was not meant to be given to them. There was no representatives' briefing material or instructions to health professionals explaining the purpose of the book. The Appeal Board noted the company's written submissions and considered that the position was unclear.

The Appeal Board considered that whatever the intended purpose of the cookbook there was a possibility that it would be given to a patient for his or her own use. In such circumstances the sticker on the back of the book would be regarded as an advertisement for a prescription only medicine to the general public in breach of the Code. The Appeal Board upheld the Panel's ruling of a breach of Clause 20.1. The appeal on this point was unsuccessful.

3 Claims: 'The future is predictable' and 'Predictable. A new basal analogue'

The claim 'The future is predictable' appeared on the inside cover of the launch box and 'Predictable. A new basal analogue' appeared on the wraparound sleeve for the cookbook.

COMPLAINT

Aventis stated that these claims were inadequately supported by the references provided. Aventis alleged that neither claim was substantiable given that at the outset of therapy, neither physician nor patient could be certain whether Levemir would require once or twice daily dosing – this did not constitute predictability. Aventis therefore alleged both claims were in breach of Clauses 7.2 and 7.4.

RESPONSE

Novo Nordisk had explained to Aventis that 'The future is predictable' was not a claim it was a strapline. 'The future' referred to the fact that Levemir was launched on 21 June, the day health professionals received the launch pack. The page taken in its entirety indicated that in the future Levemir would be available for prescribing in the UK. This strapline was not dissimilar to other commonly used commercial straplines.

Novo Nordisk noted that 'Predictable. A new basal analogue' and 'FlexPen – a new basal analogue for predictable results day after day' were currently the subject of another complaint, Case AUTH/1622/8/04, the adjudication on which was awaited.

Novo Nordisk stated that Levemir offered diabetics a predictable blood glucose profile and control. The reference cited was Heise *et al* which appeared on the front cover of the box.

Aventis' view that 'neither physician nor patient can be certain whether Levemir will require once or twice daily dosing' missed the point on predictability. Predictability referred to reduced within-patient (intra-subject) variability. This was an inherent property of an insulin, as clearly illustrated by the pharmacodynamic study reported by Heise *et al*.

Novo Nordisk stated that Aventis' complaint confused two separate issues: frequency of dosing and within-patient variability (or predictability). This was understandable as Aventis' key claim for its basal insulin, Lantus, was one injection a day (Lantus SPC). In contrast, the Levemir SPC stated that 'Levemir should be administered once or twice daily depending on patients' needs'. This gave health professionals the freedom to prescribe as they deemed fit, adjusting the frequency of daily administration to suit the patient's needs. Whether a basal insulin needed to be injected once or twice daily might therefore have become a differentiator between Lantus and Levemir in Aventis' view, and hence resulted in this complaint.

Novo Nordisk pointed out that Levemir's key claim was 'predictability', which referred not to the frequency of administration but to within-patient variability. This was a concept well accepted by health professionals. Aventis had used the word 'predictability' in its promotional materials' and had also referred to within-patient variability when explaining such use.

PANEL RULING

The Panel did not accept Novo Nordisk's submission that within the context of the page in question 'June 21st Levemir Launch Day The future is predictable' the claim 'The future is predictable' implied that 'the future' referred to was that Levemir would be available for prescribing in the UK. The Panel considered that the claim would be read within the context of the claims for predictability on the launch pack and the items within, which included the second claim at issue 'Predictable. A new basal analogue.' The box, cookbook wraparound, booklet and laminated card all referred to '...predictable results day after day' which appeared as a strapline as part of the product logo. The A4 laminated card also referred to 'a more predictable profile.' The booklet referred to 'predictable results,' a 'predictable basal insulin' and 'predictable blood glucose levels'.

The Panel noted that Novo Nordisk had referred to Case AUTH/1622/8/04, which at the date of the Panel's consideration had been adjudicated upon by the Panel but neither party had been advised of the outcome. Further the Panel noted that neither claim at issue in the present case was the subject of complaint in Case AUTH/1622/8/04; although the claim 'Levemir FlexPen (insulin determiner) predictable results day after day' was considered. Further the Panel noted that in the present case Aventis had alleged the claims at issue were misleading solely because at the outset of therapy it would not be certain whether once or twice daily dosing was required. This allegation was not considered in Case AUTH/1622/8/04.

The Panel did not consider that either claim was misleading or incapable of substantiation merely because the dosing regimen was unknown at initiation of treatment as alleged. No breach of Clauses 7.2 or 7.4 was ruled on this narrow point.

4 Format and maintenance of high standards

COMPLAINT

Aventis alleged that, overall, the launch pack, together with its contents, was in breach of Clauses 9.1 and 9.7 and that the items and claims listed above disregarded both the letter and spirit of the Code as detailed.

RESPONSE

Novo Nordisk did not respond specifically in relation to these allegations.

PANEL RULING

The Panel noted that the launch box was 41.5 x 34 x 4.5cm and was to be delivered by Novo Nordisk employees. Nonetheless the Panel considered that the size of the launch box was extreme and would cause inconvenience. It thus failed to comply with Clause 9.7 which required *inter alia* that extremes of format and size must be avoided. A breach of Clause 9.7 was ruled.

The Panel noted its rulings above but did not consider that the material in its totality failed to maintain high standards; no breach of Clause 9.1 of the Code was ruled.

Complaint received **7 September 2004**

Case completed **29 March 2005**

CASES AUTH/1637/10/04 and AUTH/1638/10/04

LILLY v GLAXOSMITHKLINE and BAYER

Promotion of Levitra

Lilly complained about a journal advertisement, two leavepieces and a poster presentation (Sommer *et al* 2003) used in the promotion of Levitra (vardenafil) by GlaxoSmithKline and Bayer Healthcare. Levitra was indicated for the treatment of erectile dysfunction (ED). Lilly marketed Cialis (tadalafil).

Lilly noted that the journal advertisement and the front page of both leavepieces featured the photograph of the head of an unstruck match angled at about 20°. Beneath the visual was the claim '*Take it for granted* there *will* be sparks'. The product logo incorporated the strapline 'Rapid and reliable in erectile dysfunction' and was preceded by the depiction of a flame.

Lilly stated that the two claims and the match visual were linked by a theme of fire. The match provided a phallic visual and sat above the claim 'Take it for granted there will be sparks'. This was linked by the Levitra flame logo to the strapline 'Vardenafil rapid and reliable in ED'. Thus the artwork and text taken together made claims that 'Levitra is rapid and reliable in ED', and that it could be taken for granted that there would be clinical efficacy for men with ED.

The ability to maintain an erection was required for a reliable, clinically useful response (efficacy) in the opinion of most men. Lilly alleged that it was misleading to suggest that efficacy could be taken for granted when the Levitra SPC listed success rates of between 1 in 2 and 4 in 5 depending on the nature of the ED treated, the presence of co-morbid conditions, the dose administered and the degree of clinical success measured. The term reliability suggested near universal success not a 1 in 2 chance of success. Lilly thus alleged that the three claims were each in breach of the Code because they were misleading, exaggerated and not compatible with the SPC. The Panel noted that the phrase 'take it for granted' meant that one could regard something as necessarily true or certain to happen. 'Rely' meant that one could depend upon something with full trust or confidence. The Panel considered that the claim '*Take it for granted* there *will* be sparks' in association with the unstruck match and the flame of the Levitra logo implied that clinical efficacy was a certainty. This implication was strengthened by the emphasis to the phrase 'Take it for granted' and the word 'will' and also by the strapline 'Rapid and reliable in ED'. The impression of certain success was further reinforced by the use of the match and flame visual in that matches were almost guaranteed to strike thus resulting in a flame. The Panel considered that the two claims and associated visuals were misleading and exaggerated; guaranteed success was inconsistent with the particulars listed in the Levitra SPC. Breaches of the Code were ruled which were upheld upon appeal by Bayer and GlaxoSmithKline.

Lilly noted the claim 'Reliable even in sildenafil non-responders (GAQ)' which appeared in one of the leavepieces. A bar chart below the claim depicted the results of Carson *et al* (2003) in which 62% of sildenafil [Viagra] (100mg) non-responders reported improved erections with Levitra. A response rate of 62%, however, meant that one third of patients failed to respond to Levitra. A failure rate of 1 in 3 was not consistent with a claim of reliability: the term reliability suggested near universal success. Lilly alleged that the claim was exaggerated.

The Panel noted that Carson *et al* was a double-blind, placebo controlled study in men with moderate to severe ED which tested the hypothesis that Levitra was efficacious and well tolerated in prior Viagra non-responders (n=231). There were three primary endpoints; the International Index of Erectile Function – Erectile Function (ILEF-EF) domain score, SEP2 (penetration) and SEP3 (maintenance of erection). The Global Assessment Questionnaire (GAQ) was a secondary endpoint. After 12 weeks' Levitra therapy the EF domain score had improved, 62.3% of men achieved SEP2 ($p<0.001$) and 46.1% achieved SEP3 ($p<0.001$). Improved erections (GAQ) were reported by 61.8% of men who took Levitra ($p<0.001$). The Panel thus noted that although two thirds of men reported improved erections with Levitra as determined by the GAQ, less than half had been able to maintain an erection long enough for complete intercourse (SEP3).

The Panel noted that the GAQ results were depicted in the leavepiece beneath the claim at issue. GAQ was a secondary endpoint. The Panel considered, given the other efficacy results of Carson *et al* and its comments above regarding the meaning of 'rely', the claim 'Reliable even in sildenafil non-responders' was exaggerated as alleged. The front page of the leavepiece, as considered above, set the tone for the whole leavepiece and strengthened the impression of near universal success. A breach of the Code was ruled which was upheld on appeal by Bayer and GlaxoSmithKline.

Lilly alleged that the claim 'Patients can rely on Levitra to work effectively for up to 5 hours', which appeared in both leavepieces, was misleading because not all patients could rely on Levitra to work at all according to the SPC and no data existed to show efficacy was achieved on every dose.

The Panel noted that the claim was referenced to the Levitra SPC which stated that the terminal half life of vardenafil was approximately 4-5 hours. The Panel noted its comments above with regard to the meaning of 'rely' and considered, contrary to the respondents' submission, that the claim 'Patients can rely on Levitra to work effectively for up to 5 hours' implied universally that the product would always work for as long as 5 hours post-dose in all patients. The Panel considered that such a claim was misleading and exaggerated as alleged and inconsistent with the particulars listed in the Levitra SPC. Breaches of the Code were ruled.

Upon appeal by Bayer and GlaxoSmithKline, the Appeal Board noted that in addition to stating that

the terminal half life of vardenafil was approximately 4-5 hours, the Levitra SPC also stated 'Across the pivotal trials, treatment with vardenafil resulted in an improvement of erectile function compared to placebo. In the small number of patients who attempted intercourse up to four to five hours after dosing the success rate for penetration and maintenance of erection was consistently greater than placebo'. Bayer was unable to answer a question from the Appeal Board relating to the percentage of patients for whom Levitra worked five hours post-dose. However the Appeal Board noted that Stief *et al* (2004b) reported that in men with ED for >6 months who received vardenafil 5, 10 or 20mg, SEP3 success 8-12 hours post-dose was between 64-86% for all three doses.

The Appeal Board considered that the claim 'Patients can rely on Levitra to work effectively for up to 5 hours' implied that the product would always work for as long as 5 hours post-dose in all patients. The Appeal Board did not consider that Stief *et al* (2004b) was sufficient to support such an assertion. The Appeal Board considered that the claim was misleading and exaggerated as alleged and inconsistent with the particulars listed in the Levitra SPC. The Appeal Board upheld the Panel's rulings of breaches of the Code.

Lilly noted that the claim 'Reliable first time – 77% success at first attempt' appeared in both leavepieces immediately below the claim 'Patients can rely on Levitra to work effectively for up to 5 hours'. 'Reliable first time' was referenced to Valiquette *et al* (2002).

Lilly stated that it was not clear what endpoint was being used here or what dose it related to. Even assuming universal first time success in responders (which was known not to be the case) the rate cited was not compatible with the SPC. The SPC gave the SEP2 response rate for the starting dose of 10mg as 76% and the SEP3 response rate as 63%. At the 20mg dose the response rates were 80% and 65% respectively.

The Panel noted the respondents' submission that in terms of the claim '… 77% success at first attempt', success was defined as SEP2. This was not made clear in the claim at issue which was thus misleading in that regard. A breach of the Code was ruled. The claim referred to a first dose response and not efficacy over a period of 3 months which was the data given in the SPC. The claim was thus not inconsistent with the particulars listed in the SPC. No breach of the Code was ruled.

Lilly noted that the 2004 BAUS (British Association of Urological Surgeons) printed exhibition guide encouraged delegates to visit Bayer's stand to request information on patient preference. In response a copy of a poster presentation by Sommer *et al* (2003) was provided. Lilly considered that because this request for information was solicited, the poster should be regarded as promotional material. Lilly stated that the poster was not accompanied by the prescribing information and nor had it been peer reviewed. The potential limitations of the study had not been highlighted including the fact that only interim data was presented reflecting only a quarter of the study population, the study was open-label and subjects were given a very short trial of each therapy (just 4 tablets). Lilly alleged that failure to highlight these limitations made the claims and comparisons misleading and unfair.

The Panel noted that the Sommer *et al* poster was available from the Bayer stand at the BAUS meeting. Delegates had been told that copies of the poster would be available. The Panel thus considered that Bayer and GlaxoSmithKline had solicited requests for the poster and were seeking to use it for a promotional purpose. The poster referred to Levitra but did not include prescribing information. The Panel ruled a breach of the Code. The Panel considered that as the provision of the poster was solicited the clause in the Code relating to the unsolicited provision of articles had not been breached. Upon appeal by Bayer and GlaxoSmithKline, the Appeal Board upheld the Panel's ruling of a breach of the Code.

The Panel noted that GlaxoSmithKline and Bayer had not responded to Lilly's comments with regard to the limitations of Sommer *et al*. The poster presentation did not state how long the study had lasted nor that only interim data were presented. Given the respondent's use of the poster it had to be regarded as a piece of promotional material. The Panel thus considered that the comparisons made in the poster were misleading and unfair. Breaches of the Code were ruled.

Upon appeal by Bayer and GlaxoSmithKline the Appeal Board did not consider that the poster made it sufficiently clear as to the length of the study period or that it was an ongoing study with data in 86/237 patients in the maximum dose trial and 47/211 in the half maximum dose trial presented. The primary endpoints related to efficacy measurements and in addition patient satisfaction and preference were assessed. The Appeal Board noted the results from Porst *et al* (2003) which assessed patient preference and favoured tadalafil. Given the respondent's use of the poster it had to be regarded as a piece of promotional material. The Appeal Board thus considered that the comparisons made in the poster were misleading and unfair and upheld the Panel's rulings of breaches the Code.

Eli Lily and Company Limited complained about the promotion of Levitra (vardenfil) by GlaxoSmithKline UK Limited and Bayer Healthcare. Levitra was indicated for the treatment of erectile dysfunction (ED). Correspondence between the parties had failed to resolve the issues. The items at issue were a journal advertisement (ref 4LEVI191) and two leavepieces (refs 4LEVI216 and 4LEVI197). Lilly was also concerned about the distribution of a poster presentation (Sommer *et al* 2003).

Lilly marketed Cialis (tadalafil).

A The journal advertisement and the leavepieces

The journal advertisement and the front page of both leavepieces all had the same artwork and claims. All

featured the photograph of the head of an unstruck match angled at about 20°. Beneath the visual was the claim '**Take it for granted** there **will** be sparks'. The product logo incorporated the strapline 'Rapid and reliable in erectile dysfunction' and was preceded by the depiction of a flame.

1 Claims '*Take it for granted* there *will* be sparks' and 'Rapid and reliable in erectile dysfunction'

COMPLAINT

Lilly stated that the three elements (the two claims and the match visual) were linked by a theme of fire. The match was drawn so as to provide a phallic visual and sat above the claim '**Take it for granted** there **will** be sparks'. This was linked by the Levitra flame logo to the strapline 'Vardenafil rapid and reliable in ED'. Thus the artwork and text taken together made claims that 'Levitra is rapid and reliable in ED', and that it could be taken for granted that there would be clinical efficacy for men with ED.

Lilly considered that it was misleading to state that there would be sparks (efficacy) given that the Levitra summary of product characteristics (SPC) listed the following success rates:

'In fixed dose studies in a broad population of men with erectile dysfunction, 68% (5mg), 76% (10mg) and 80% (20mg) of patients experienced successful penetrations (SEP2) … the ability to maintain the erection (SEP3) in this broad ED population was given as 53% (5mg), 63% (10mg) and 65% (20mg) … in pooled data from the major efficacy trials, the proportion of patients experiencing successful penetration on vardenafil were as follows: psychogenic erectile dysfunction (77-87%), mixed erectile dysfunction (69-83%), organic erectile dysfunction (64-75%), elderly (52-75%), ischaemic heart disease (70-73%), hyperlipidemia (62-73%), chronic pulmonary disease (74-78%), depression (59-69%), and patients concomitantly treated with antihypertensives (62-73%) … in a clinical trial in patients with diabetes mellitus, vardenafil significantly improved the erectile function domain score, the ability to obtain and maintain an erection long enough for successful intercourse and penile rigidity compared to placebo at vardenafil doses of 10mg and 20mg … the response rates for the ability to obtain and maintain an erection was 61% and 49% on 10mg and 64% and 54% on 20mg.'

The ability to maintain an erection would be required for a reliable, clinically useful response (efficacy) in the opinion of most men. Lilly considered that it was misleading to suggest that efficacy could be taken for granted given the success rates listed in the SPC. Clearly not every patient taking Levitra would experience efficacy.

Lilly considered that it was misleading to claim reliability of effect when the Levitra SPC listed success rates of between 1 in 2 and 4 in 5 depending on the nature of the ED treated, the presence of co-morbid conditions, the dose administered and the degree of clinical success measured. The term reliability suggested near universal success not a 1 in 2 chance of success.

As a result Lilly alleged that the three claims outlined above were each in breach of Clauses 7.2, 7.10 and 3 of the Code because they were misleading, exaggerated and not compatible with the wording of the SPC.

RESPONSE

The companies noted that Levitra was licensed for the treatment of ED, which was the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance. Levitra had never been promoted for anything except ED in the UK and therefore the contention that there had been a breach of Clause 3 was not valid.

GlaxoSmithKline and Bayer stated that before demonstrating that the claims at issue were neither misleading nor exaggerated, nor that they must be restricted to figures quoted in the SPC where new data had since become available, it was important to set the context of what was regarded as 'normal', and able to be taken for granted, sexual function in males aged 50+.

Although not necessarily a function of ageing, sexual activity and erectile function in middle-aged and elderly men tended to be different from those of young men. Whilst men in their twenties might expect to have perfect erectile function whenever sexual activity was attempted, older men occasionally experienced some degree of ED. In a large cohort study of 1290 normal men over the age of 40, 52% were found to have some degree of ED (Feldman *et al* 1994).

Clinical trials in ED typically recruited men in late middle age. When considering the outcomes of such trials, it was thus more reasonable to hope for restoration of erectile function to the level of 'normal' men in this age group, rather than restoring the function they enjoyed decades earlier. Studies of vardenafil had shown success by a variety of measures. Attaining an erection that was hard enough for vaginal penetration occurred in 80-90% of occasions (SEP2); attaining an erection that was maintained long enough for complete intercourse (SEP3) was achieved on 65-80% of occasions (Stief *et al* 2004a; Potempa *et al* 2004; Hellstrom *et al* 2002). Therefore, what could be 'taken for granted' by men with ED who took vardenafil was the kind of erectile function that they enjoyed until relatively recently.

With regard to the claim '**Take it for granted** there **will** be sparks' GlaxoSmithKline and Bayer stated that in essence, efficacy rates quoted in the Levitra SPC were derived from registration studies and were necessarily conducted relatively early in the product's life-cycle. As stated in the SPC, SEP2 results ranged from 68-80% and SEP3 from 53-65%, which was a significant improvement in this population. Subsequent studies designed to more closely reflect clinical practice might provide efficacy data which were different from the data submitted for registration but which were nonetheless valid for the substantiation of promotional claims.

The RELY study (Valiquette *et al* 2004), was designed to evaluate and confirm the reliability of vardenafil.

Six hundred men with ED were given a single dose of vardenafil 10mg. Those with a successful response (87%), as measured by SEP2 (penetration), were randomised to receive vardenafil 10mg or placebo for 12 weeks. Subsequent SEP2 reliability rates for vardenafil-treated patients (83%) were determined as the percentage of successful attempts over the total valid attempts.

Stief *et al* (2004a) was a double-blind, fixed dose, parallel group study and was closer to that of the pivotal studies quoted in the SPC ie it employed a fixed-dose protocol whereby responses to doses of 10mg and 20mg of vardenafil were compared. Stief *et al* showed SEP2 results with the 20mg dose in the intention-to-treat population of ~90%, giving further substantiation to the claims. This success rate was not only seen early in the study (4 weeks after starting treatment), but was unchanged in men who were followed up for 2 years. These data showed that in this population clinical trials could substantiate a return to what could be considered as near normal.

With regard to the claim 'Rapid and reliable in ED', GlaxoSmithKline and Bayer stated that the studies cited were representative of the Levitra clinical data. In particular the references that supported the claim 'reliable'. Reliability could be interpreted as first time success as well as subsequent success rate.

Valiquette *et al* (2002) was a poster presentation of a post-hoc analysis of one of the pivotal phase III studies quoted in the SPC. It analysed success rates, as measured by SEP2, following first doses of vardenafil 5mg, 10mg or 20mg. Success rates were between 67% and 77%. In these patients, who were successful at the first dose, the reliability of vardenafil was demonstrated by continued success (as measured by SEP2) in up to 91% of patients at week 12, which was in line with normality for this population as described earlier. The reliability of vardenafil was further demonstrated in the RELY study (Valiquette *et al* 2004) and Stief *et al* as described above.

GlaxoSmithKline and Bayer submitted that neither '**Take it for granted**, there **will** be sparks' nor 'Rapid and reliable in erectile dysfunction' required reference to success rates over and above what one would expect success to be in normal men of this age group. The claims were not misleading or exaggerated.

PANEL RULING

The Panel noted that the phrase 'take it for granted' meant that one could regard something as necessarily true or certain to happen. 'Rely' meant that one could depend upon something with full trust or confidence (ref Shorter Oxford English Dictionary).

The Panel considered that the claim '**Take it for granted** there **will** be sparks' in association with the unstruck match and the flame of the Levitra logo implied that clinical efficacy was a certainty. This implication was strengthened by the emphasis to the phrase 'Take it for granted' and the word 'will' and also by the strapline 'Rapid and reliable in ED'. The impression of certain success was further reinforced by the use of the match and flame visual in that matches were almost guaranteed to strike thus resulting in a flame.

The Panel considered that the two claims and associated visuals were misleading and exaggerated; guaranteed success was inconsistent with the particulars listed in the Levitra SPC. Breaches of Clauses 3.2, 7.2 and 7.10 were ruled.

APPEAL BY BAYER AND GLAXOSMITHKLINE

Bayer was concerned that the Panel seemed to take the view that promotional claims could only be substantiated by reference to studies quoted in a product's SPC. This was hard to reconcile with Clause 3.2, which stated that 'Information, claims … must be based on an up-to-date evaluation of all the evidence …'. It seemed to Bayer that not only were companies allowed to report evidence subsequent to the regulatory studies, they were obliged to do so.

Bayer noted that it had referred to a number of recent studies which substantiated the claim that Levitra was reliable and which were referenced on the materials in question; the Panel's ruling seemed not to have taken this into account. Bayer requested clarification on this issue since it seemed key to the Panel's rulings.

Bayer submitted that the Panel's interpretation of the word 'reliable', albeit based on a dictionary definition, was over rigorous and not consistent with common usage or understanding. In the context of medicines (or biological systems in general), nothing happened 100% of the time: this did not mean that a medicine with efficacy of less than 100% could not be described as reliable. In the context of treatments for ED, efficacy (and therefore reliability) could be described in a number of different ways including response to the first dose, continued response over time, speed of onset after taking a tablet and improvement on previous medication. All of these might be equally valid for different patients and data in these areas would generally not be included on an SPC.

The Levitra campaign in question ('rapid and reliable') attempted to characterise the various facets of the reliability of Levitra in ED and Bayer submitted that it was justified in making the claims.

Bayer noted that the claim '**Take it for granted** there **will** be sparks' appeared in conjunction with the image of an unstruck match and a flame which was part of the Levitra logo.

Bayer reiterated that middle aged or elderly men with ED might have a different perspective as to what could be 'taken for granted' in terms of erectile function. Bayer submitted that in the context of sexual activity and expectations in this group of men, Levitra's efficacy could be 'taken for granted'. The veracity of this phrase did not depend on reported success rates of 100%, something that was surely impossible for any medicine.

With regard to the claim 'Rapid and reliable in erectile dysfunction', Bayer noted that it had referred to studies that indicated higher levels of efficacy than those reported in the Levitra SPC, with success rates of 80-90%. These included a recent study showing that 87% of men with ED responded to the first dose.

The Panel appeared to make no reference to these points and therefore it was pertinent to reiterate them. The high levels of efficacy seen in clinical trials with Levitra since registration justified the claims that Levitra was 'reliable'. Again the veracity of this phrase did not depend on reported success rates of 100%.

The ruling of a breach of Clauses 3.2, 7.2 and 7.10 was not justified.

COMMENTS FROM LILLY

Lilly considered that the combined effect of the claims and artwork overstated the clinical efficacy of Levitra, in breach of Clauses 7.2, 7.10 and 3.2, by the deliberate blurring between efficacy and reliability.

Lilly concurred with the Panel that the common understanding of 'reliable' was as per the Oxford English Dictionary. 'Rely: one could depend upon something with full trust or confidence'. The definition of efficacy on the other hand was the 'ability to produce a desired or intended result' (ref The Compact Oxford English Dictionary). Lilly disagreed with Bayer that 'reliable' was open to interpretation without appropriate qualification. As Bayer stated 'nothing in medicine happened 100% of the time'. It was for this very reason that the claims should be found in breach.

Lilly noted Bayer's submission that the claim '**Take it for granted** there **will** be sparks' should be taken within the context of men with ED. The suggestion therefore was that the 'sparks' experienced by men with ED on Levitra would be different from the 'sparks' experienced in men without ED. There was no substantiation provided to support this. Lilly argued that this did not detract from the impression of clinical certainty given, by this claim, to men with ED and their GPs.

The claim 'Rapid and reliable in erectile dysfunction' was referenced to three posters. Stief *et al* (2003) was a double-blind, fixed dose trial which sub-selected likely responders and therefore not representative of the general population of men with ED. 1020 men were randomised to an initial 12 months of treatment. While 755 men completed the study, only 566 were entered in the subsequent 12 months of treatment, with 479 completing the study. Therefore less than half of the initial study population completed two years of continuous therapy. Lilly argued that it was highly likely that only responders remained and again questioned why efficacy in such men was not 100%. This study had subsequently been published (Stief *et al* 2004a) and the discussion section commented that the design of the study 'could have resulted in 'enrichment' of the study population with patients who had a favourable response to vardenafil'. Furthermore this study was not placebo-controlled. Every patient received active and placebo in combination; this allowed blinding with respect to the dose but was a source of potential bias since all patients knew they were on active treatment. The poster stated that 'All qualitative efficacy variables were presented as descriptive statistics and no statistical conclusions were drawn from the results'. Lilly concluded that these data provided insufficient substantiation of the claim.

Valiquette *et al* (2002), was a retrospective analysis of a fixed dose, placebo-controlled trial of 805 men with ED. The design and population were similar to Hellstrom *et al*. As stated in the paper, there were two potential limitations to the study; the exclusion of patients who failed on sildenafil therapy and the imbalance between the 20% of patients in the placebo group who discontinued due to lack of effect and the 7% who discontinued in the vardenafil group for the same reason. The LOCF employed in analysing the erectile function domain data, SEP2 and SEP3, from which the conclusions of the poster were drawn, might be subject to bias.

Finally Stief *et al* (2004b) was a pooled analysis of two randomised, double-blind phase 3 studies of similar methodology to that of Hellstrom *et al* and Valiquette *et al*. No absolute numbers were given to confirm that it was the same population of patients. Efficacy was measured by percentage 'yes' responses to SEP3 (successful intercourse) and varied between 52% and 86%. The title suggested that vardenafil improved erections from 15 minutes after dosing, however patients were instructed to start sexual activity one hour after dosing. It was unclear from the abstract how the conclusions were derived.

More recently, the introduction to the RELY study (Valiquette *et al* 2004) stated that 'one of the most important features for patient satisfaction with an ED therapy is that it works reliably every time', which was consistent with Lilly's arguments. This double-blind trial only randomised responders to vardenafil 10mg. Lilly stated that this was not a representative population of all men with ED. Indeed it was surprising that first time success rates of 87% on 10mg were not actually 100% as all these patients responded to the medicine. Furthermore Bayer quoted a successful response as SEP2 (penetration). Lilly argued that the most clinically relevant endpoint was SEP3 (ability to complete intercourse). This data appeared in abstract form only and had not been peer reviewed. For these reasons it was not sufficiently robust to substantiate the claims.

Lilly noted that Bayer had cited Potempa *et al*, which evaluated efficacy during 10 weeks of treatment in 398 men. This was a single arm, open label study and therefore not as scientifically rigorous as a double-blind placebo-controlled trial. Lilly argued that efficacy claims derived from this study should be viewed within that context.

The final paper quoted was Hellstrom *et al*, a phase 3 randomised, double-blind, placebo-controlled fixed dose comparison of Levitra 5, 10 and 20mg. The limitations of this paper were discussed above. This paper, however, quoted figures consistent with the SPC (percentage of 'yes' responses to SEP2, 76% and SEP3, 65% for vardenafil 10mg, percentage of 'yes' responses to SEP2, 81% and SEP3, 66% for vardenafil 20mg) but did not substantiate the claim in question.

With regard to the ruling of a breach of Clause 3.2, Lilly recognised the value and role of post-registration studies, but that there were potential problems in using such data alone.

The SPC represented the integral qualities of a medicine. Hence the fundamental efficacy of Levitra

was as stated in the SPC. Whilst data from post-registration trials could be used to support and augment the fundamental data contained in the SPC, Lilly argued that it must be presented within this context, with clear reference to the underlying data. The efficacy data contained in the SPC did not appear anywhere in the promotional material.

While Lilly agreed with Bayer that claims must be based on an up-to-date evaluation of all the evidence, it did not believe that this invalidated the fundamental requirement of the Code that the promotion of a medicine must not be inconsistent with its SPC. Furthermore, evaluation of all data supporting promotional claims must recognise and reflect potential limitations of those data. This had not been the case in these promotional pieces. This was well demonstrated by Stief *et al* (2003) which, when subjected to peer review and publication (Stief *et al* 2004a), highlighted the potential 'enrichment' of the study population with patients who had a favourable response to vardenafil. Lilly concluded, given the limitations of the studies as outlined above, that the data were insufficiently robust to support the claims made.

APPEAL BOARD RULING

The Appeal Board considered that the claim '**Take it for granted** there **will** be sparks' in association with the unstruck match and the flame of the Levitra logo implied that clinical efficacy was a certainty. This implication was strengthened by the emphasis to the phrase 'Take it for granted' and the word 'will' and also by the strapline 'Rapid and reliable in ED'. The impression of certain success was further reinforced by the use of the match and flame visual in that matches were almost guaranteed to strike thus resulting in a flame.

The Appeal Board noted that the studies which had reported higher success rates than those reported in the SPC had included selected patient groups and that some of the reported success rates of 80-90% related to SEP2 (penetration) and not SEP3 (maintenance of erection).

The Appeal Board considered that the two claims and associated visuals were misleading and exaggerated; guaranteed success was inconsistent with the particulars listed in the Levitra SPC. The Appeal Board upheld the Panel's ruling of breaches of Clauses 3.2, 7.2 and 7.10. The appeal on this point was unsuccessful.

2 Claim 'Reliable even in sildenafil non-responders (GAQ)'

This claim appeared in one of the leavepieces (ref 4LEVI197) and was headed 'New data'. A bar chart below the claim depicted the results of Carson *et al* (2003) in which 62% of sildenafil [Viagra] (100mg) non-responders reported improved erections with Levitra

COMPLAINT

Lilly noted the claim that Levitra was reliable even in sildenafil non-responders, however the response rate of 62% meant that 1 in 3 of the study patients failed to respond to Levitra. A failure rate of 1 in 3 was not consistent with a claim of reliability: the term reliability suggested near universal success. Lilly alleged that the claim at issue was therefore exaggerated in breach of Clause 7.10 of the Code.

RESPONSE

GlaxoSmithKline and Bayer considered that Lilly's interpretation of reliable as near universal success was unreasonable considering the severity of the condition in these men. In Carson *et al* all patients had a history of unresponsiveness to sildenafil; they were subsequently treated with Levitra in a flexible dose manner. The respondents regarded 62% success in patients who had previously failed to respond to sildenafil as reliable.

PANEL RULING

The Panel noted that Carson *et al* was a double-blind, placebo controlled study in men with moderate to severe ED which tested the hypothesis that Levitra was efficacious and well tolerated in prior Viagra non-responders (n=231). There were three primary endpoints; the International Index of Erectile Function – Erectile Function (ILEF-EF) domain score, SEP2 and SEP3. The Global Assessment Questionnaire (GAQ) was a secondary endpoint. After 12 weeks' Levitra therapy the EF domain score had improved, 62.3% of men achieved SEP2 ($p<0.001$) and 46.1% achieved SEP3 ($p<0.001$). Improved erections (GAQ) were reported by 61.8% of men who took Levitra ($p<0.001$). The Panel thus noted that although two thirds of men reported improved erections with Levitra as determined by the GAQ, less than half had been able to maintain an erection long enough for complete intercourse (SEP3).

The Panel noted that the GAQ results were depicted in the leavepiece beneath the claim at issue. GAQ was a secondary endpoint. The Panel considered, given the other efficacy results of Carson *et al* and its comments regarding the meaning of 'rely' at point 1 above, the claim 'Reliable **even** in sildenafil non-responders' was exaggerated as alleged. The front page of the leavepiece, as considered in point 1 above, set the tone for the whole leavepiece and strengthened the impression of near universal success. A breach of Clause 7.10 was ruled.

APPEAL BY BAYER AND GLAXOSMITHKLINE

Bayer submitted that the argument rested with the interpretation of 'reliable' in the context of therapies for ED, in this instance involving men who had already failed consistently on a previous therapy. For this group of disappointed men, improved erections in 62% could be seen as reliable, compared to their previous experience with sildenafil. Bayer disagreed with the Panel's comment that the leavepiece as a whole and the claim in particular gave the impression of 'near universal success'. A breach of Clause 7.10 was denied.

COMMENTS FROM LILLY

Lilly stated that Carson *et al* had attracted much criticism because of the criteria used to define a sildenafil failure. Lilly noted the editorial comments on the paper that 'in the absence of a sildenafil rechallenge, … one cannot be entirely confident that the patients would have remained unresponsive to sildenafil'. McCullough *et al* (2002) showed that 55% of men who were previously unsuccessful with sildenafil became successful after re-education and counselling. The editorial also noted 'that from a scientific viewpoint it is difficult to reconcile why two agents with such structural, biochemical and pharmacokinetic similarities as sildenafil and vardenafil should have such divergent profiles of clinical efficacy. On this basis, the concept that most patients in whom sildenafil fails will be salvaged by administration of vardenafil (rather than continuation of sildenafil) would be best considered to fall under the Scottish Law terminology of being 'not proven'.

APPEAL BOARD RULING

The Appeal Board noted that Carson *et al* reported that only 46.1% of prior sildenafil non-responders had been able to maintain an erection long enough for complete intercourse (SEP3) when treated with Levitra. The Appeal Board thus considered that the claim 'Reliable **even** in sildenafil non-responders' was exaggerated as alleged. The front page of the leavepiece, as considered in point 1 above, set the tone for the whole leavepiece and strengthened the impression of near universal success. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.10. The appeal on this point was unsuccessful.

3 Claim 'Patients can rely on Levitra to work effectively for up to 5 hours'

This claim appeared in both leavepieces.

COMPLAINT

Lilly alleged that the claim was misleading because not all patients could rely on Levitra to work at all according to the SPC and no data existed to show efficacy was achieved on every dose. Lilly alleged breaches of Clauses 3, 7.2 and 7.10 of the Code.

RESPONSE

GlaxoSmithKline and Bayer submitted that the claim was based upon data in the SPC that was derived from registration studies. The phrase 'up to 5 hours' had been used specifically to emphasise that this was not a universal claim that Levitra was effective for all patients on every occasion at every dose. The companies noted that Stief *et al* (2004b) had shown that Levitra exhibited clinical efficacy up to 12 hours after ingesting a tablet.

PANEL RULING

The Panel noted that the claim at issue was referenced to the Levitra SPC which stated that the terminal half life of vardenafil was approximately 4-5 hours.

The Panel noted its comments at point 1 above with regard to the meaning of 'rely' and considered, contrary to the respondents' submission, that the claim 'Patients can rely on Levitra to work effectively for up to 5 hours' implied universally that the product would always work for as long as 5 hours post-dose in all patients. The Panel considered that such a claim was misleading and exaggerated as alleged and inconsistent with the particulars listed in the Levitra SPC. Breaches of Clauses 3.2, 7.2 and 7.10 were ruled.

APPEAL BY BAYER AND GLAXOSMITHKLINE

Bayer stated that whilst the SPC stated that the terminal half-life of vardenafil was approximately 4-5 hours, this was not the justification for the claim. Rather, it referred to patients in the pivotal studies who attempted sexual activity up to 5 hours after dosing, in whom the effects of Levitra were consistently greater than placebo.

As previously stated, the words 'up to 5 hours' were deliberately used so as not to misleadingly suggest that all patients would respond at 5 hours. It appeared that the Panel interpreted the words 'up to' to mean that the product would always work for as long as 5 hours post-dose in all patients at all doses and Bayer submitted that a different interpretation was reasonable. The company denied breaches of Clauses 3.2, 7.2 and 7.10.

COMMENTS FROM LILLY

Lilly agreed with the Panel that the claim was in breach of Clauses 3.2, 7.2 and 7.10 as there were no data confirming efficacy for every patient or for every dose.

While the claim was clearly referenced to the SPC, Bayer conceded that this was not the justification for the claim and referred 'to patients in pivotal studies who attempted intercourse up to 5 hours after dosing, in whom the effects of Levitra were consistently greater than placebo'. No reference was given for these studies.

Lilly noted Bayer's submission that the phrase 'up to 5 hours' was 'deliberately used so as not to suggest that all patients would respond in 5 hours'. 'Up to 5 hours' referred to time. The sentence began with the phrase 'Patents can rely on Levitra' and this was the central claim at issue. It was this exaggerated tone that coloured the whole piece. Overall the appeal did not acknowledge that not all patients nor all doses would produce clinical efficacy as suggested by the claim.

APPEAL BOARD RULING

The Appeal Board noted that the claim at issue was referenced to the Levitra SPC which stated that the terminal half life of vardenafil was approximately 4-5 hours. The SPC also stated 'Across the pivotal trials, treatment with vardenafil resulted in an improvement of erectile function compared to placebo. In the small number of patients who attempted intercourse up to four to five hours after dosing the success rate for penetration and maintenance of erection was

consistently greater than placebo'. Bayer was unable to answer a question from the Appeal Board relating to the percentage of patients for whom Levitra worked five hours post-dose.

The Appeal Board noted an abstract by Stief *et al* (2004b) a pooled analysis of two pivotal randomised, double-blind phase 3 studies in which men with ED for >6 months received vardenafil 5, 10 or 20mg or placebo for 12 or 26 weeks. SEP3 success 8-12 hours post-dose was between 64-86% for all three doses.

The Appeal Board considered, contrary to the respondents' submission, that the claim 'Patients can rely on Levitra to work effectively for up to 5 hours' implied that the product would always work for as long as 5 hours post-dose in all patients. The Appeal Board did not consider that Stief *et al* (2004b) was sufficient to support such an assertion. The Appeal Board considered that such a claim was misleading and exaggerated as alleged and inconsistent with the particulars listed in the Levitra SPC. The Appeal Board upheld the Panel's rulings of breaches of Clauses 3.2, 7.2 and 7.10. The appeal on this point was unsuccessful.

4 Claim 'Reliable first time – 77% success at first attempt'

This claim appeared in both leavepieces immediately below the claim at issue in point A3 above. 'Reliable first time' was referenced to Valiquette *et al* (2002).

COMPLAINT

Lilly stated that it was not clear what endpoint was being used here (SEP2 or SEP3 or some other endpoint) or what dose it related to. Even assuming universal first time success in responders (which was known not to be the case in the management of ED) the rate cited was not compatible with the SPC. The SPC gave the SEP2 response rate for the starting dose of 10mg as 76% and the SEP3 response rate as 63%. At the 20mg dose the response rates were 80% and 65% respectively. Lilly alleged breaches of Clauses 3 and 7.2 of the Code.

RESPONSE

GlaxoSmithKline and Bayer stated that the figure of 77% was for the first attempt using the 10mg dose, as assessed by SEP2 (penetration), stated in Valiquette *et al*. The companies noted that Lilly had cited the SEP2 and SEP3 response rates from the SPC: these were of course not response rates to the first dose, but rather the mean success rates of the study population at the end of a 12 week study.

This claim was no longer used as current data suggested success rates of up to 87% after the first dose (Valiquette *et al* 2004).

PANEL RULING

The Panel noted the respondents' submission that in terms of the claim '… 77% success at first attempt', success was defined as achieving SEP2. This was not made clear in the claim at issue which was thus misleading in that regard. A breach of Clause 7.2 was ruled. The claim referred to a first dose response and not efficacy over a period of 3 months which was the data given in the SPC. The claim was thus not inconsistent with the particulars listed in the SPC. No breach of Clause 3.2 was ruled.

B Use of a poster presentation by Sommer *et al*

COMPLAINT

Lilly noted that at the 2004 BAUS (British Association of Urological Surgeons) annual meeting, the printed exhibition guide encouraged delegates to visit Bayer's stand to request information on patient preference. In response to this request they were given a copy of a poster presentation by Sommer *et al* (2003). Lilly considered that because this request for information was solicited, the poster should be regarded as promotional material.

Lilly alleged that the poster was not accompanied by the prescribing information in breach of Clause 4.1 and nor had it been peer reviewed in breach of Clause 11.1. Because it had not been peer reviewed the potential limitations of the study had not been highlighted. These limitations included the fact that only interim data was presented reflecting only a quarter of the study population, the study was open-label and subjects were given a very short trial of each therapy (just 4 tablets). Lilly alleged that failure to highlight these limitations made the claims and comparisons misleading and unfair in breach of Clauses 7.2 and 7.3.

RESPONSE

GlaxoSmithKline and Bayer submitted that the short piece in the BAUS programme, written by Bayer, encouraging delegates to visit the Bayer stand stated: 'Bayer (in partnership with GlaxoSmithKline) will have an exhibition devoted to Levitra (vardenafil), a PDE5 inhibitor for the management of erectile dysfunction. Information on recent studies with Levitra, including patient preference, will be available on the stand'.

The delegates were invited to visit the Bayer/GlaxoSmithKline stand where the poster was available for those who showed interest in the data. The respondents contended that the poster was not an unsolicited item, it could not be regarded as promotional and thus there was no breach of the Code. GlaxoSmithKline and Bayer noted that there were copies of the Levitra SPC available at all the contact points on the stand.

PANEL RULING

The Panel noted that the Sommer *et al* poster was available from Bayer's stand at the BAUS meeting; delegates had been told that copies of it would be available. The Panel thus considered that Bayer and GlaxoSmithKline had solicited requests for the poster and were seeking to use it for a promotional purpose. The poster referred to Levitra but did not bear prescribing information for the product. The Panel ruled a breach of Clause 4.1 of the Code. It was not

sufficient to meet the requirements for providing prescribing information as set out in Clause 4 simply to have copies of the Levitra SPC available on the stand. Clause 11.1 of the Code referred to the provision of unsolicited articles, the Panel however considered that the provision of the poster was solicited and it thus ruled no breach of Clause 11.1.

The Panel noted that GlaxoSmithKline and Bayer had not responded to Lilly's comments with regard to the limitations of Sommer *et al*. The poster presentation did not state how long the study period had lasted nor that only interim data were presented. Given the respondent's use of the poster it had to be regarded as a piece of promotional material. The Panel thus considered that the comparisons made in the poster were misleading and unfair. Breaches of Clauses 7.2 and 7.3 were ruled.

APPEAL BY BAYER AND GLAXOSMITHKLINE

Bayer noted the Panel's comment that the poster did not state how long the study period had lasted. Bayer noted that in the bottom left hand corner of the poster there was an illustration of the study protocol, under which it was stated that 'After six weeks, and a wash-out period of one week, medication was changed according to the protocol. To be able to directly compare all 3 medications another 6-week treatment period was initiated after the first 4 treatment periods'.

Taken with the illustration of the study protocol, showing how many treatment periods and wash-out periods were used, Bayer submitted that it was clear how long the study had lasted.

Bayer submitted that it was not quite correct for Lilly to state that the data presented in the study were only interim: they were in fact preliminary. This was made clear in the poster, where the authors stated that the half-maximum dose (currently recommended starting dose) study was in 211 men and the maximum dose study was in 237 men but went on to state that 'presently 86 and 47 men have **completed** the maximum and half-maximum dose trials'. This was further clarified in the tables of results for the patient preference data. Bayer submitted that this was entirely different from true interim results, where for example, data were reported for all patients before the planned completion time of the study.

Bayer noted that Sommer *et al* had presented data for those patients who had completed the two studies and it was therefore reasonable to use these preliminary data on promotional items. It would be misleading to label the data as 'interim results' since strictly, they were not interim results for the patients reported.

Bayer noted that patient preference was not listed as a primary endpoint. However, in the introduction to the paper, the authors stated 'The question of which PDE5-inhibitor is preferred by the patient remains unanswered. The purpose of this study was to find an answer'. It was therefore reasonable to present the patient preference data as reported in the poster.

Bayer submitted that since these data were presented at a recognised International Congress (ESSM 2003) as a poster, they were *de facto* in the public domain and could be used to support promotional claims. Bayer disagreed that the comparison was unbalanced or capable of misleading health professionals.

COMMENTS FROM LILLY

Lilly remained unchanged in its arguments against the distribution and use of Sommer *et al*.

A printed exhibition guide encouraged delegates to visit Bayer's stand at BAUS 2004 and solicit material on patient preference for Levitra. The Sommer *et al* was distributed from the stand but was not accompanied by prescribing information. The Sommer *et al* was promotional material since health professionals were incited by Bayer to request it at the stand. Clause 4.1 stated that prescribing information must form part of the promotional material and Lilly concurred with the Panel's ruling of a breach of Clause 4.1.

Lilly concurred with the Panel's ruling that the comparisons made in the poster were misleading and unfair. The study, as described in the poster, was a comparative, randomised, multicenter study of sildenafil, tadalafil and vardenafil. The stated primary endpoints were efficacy assessments ie the change from baseline in the international Index of Erectile Function (IIEF) questions 3 and 4. It was important to note that treatment preference was not a primary endpoint of this study. A total of 237 men were enrolled in the study arm examining maximum dose sildenafil, tadalafil and vardenafil while 211 men were enrolled in the study arm comparing 50mg sildenafil, 10mg tadalafil and 10mg vardenafil (half-maximum dose). As stated in the poster, 'presently 86 and 47 men have completed the maximum and half-maximum dose trials'. Therefore the results represented 36% and 22% of each study population respectively. Lilly considered that Bayer's submission that these results were preliminary rather than interim was an issue of semantics. The data were an incomplete reflection of the total study population.

Lilly alleged that furthermore, data from Sommer *et al* were at variance with data from the only other presented study assessing patient preference for one of the three PDE5 inhibitors, Porst *et al* (2003). The supplementary information to Clause 7.2 of the Code commented specifically on the issue of variance in clinical or scientific opinion by stating 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 in promotional material.

Porst *et al* assessed patient preference for sildenafil, tadalafil and vardenafil. One hundred and fifty patients were exposed to all three medicines, starting with the mid dose and titrating according to clinical need. Overall patient preference for each medicine was: sildenafil 13%; tadalafil 45%; vardenafil 30%. 12% of patients expressed no preference. Results from all 150 patients were accounted for and the authors concluded that 'the overwhelming majority of the patients prefer the two new drugs' (tadalafil and vardenafil) 'with tadalafil being ahead due to its long duration of action'.

Sommer *et al* represented an open label ongoing study that Lilly considered was insufficiently robust to accurately support claims of patient preference for vardenafil. In addition, no care had been taken to ensure that the issue of patient preference for individual PDE5 inhibitors was treated in a balanced and fair manner as was required by the Code.

APPEAL BOARD RULING

The Appeal Board noted that Sommer *et al* was available from the Bayer stand at the BAUS meeting. Delegates had been told that copies of the poster would be available. The Appeal Board thus considered that Bayer and GlaxoSmithKline had solicited requests for the poster and were seeking to use it for a promotional purpose. The poster referred to Levitra but did not bear prescribing information for the product. The Appeal Board upheld the Panel's ruling of a breach of Clause 4.1 of the Code. The appeal on this point was unsuccessful.

The Appeal Board did not consider that the poster made it sufficiently clear as to the length of the study period or that it was an ongoing study with the data in 86/237 patients in the maximum dose trial and 47/211 in the half maximum dose trial presented. The primary endpoints related to efficacy measurements and in addition patient satisfaction and preference were assessed. The Appeal Board noted the results from Porst *et al*. Given the respondent's use of the poster it had to be regarded as a piece of promotional material. The Appeal Board thus considered that the comparisons made in the poster were misleading and unfair and upheld the Panel's rulings of breaches of Clauses 7.2 and 7.3. The appeal on this point was unsuccessful.

Complaint received **8 October 2004**

Cases completed

Case AUTH/1637/10/04 **31 March 2005**

Case AUTH/1638/10/04 **30 March 2005**

CASE AUTH/1648/11/04

GENERAL PRACTITIONER v PFIZER

Celebrex 'Dear Healthcare Professional' letter

A general practitioner stated that a 'Dear Healthcare Professional' letter about Celebrex (celecoxib) issued by Pfizer, and signed by its medical director, could only be regarded as a cynical exercise aimed at promoting Celebrex in the guise of a safety update on COX-2 selective inhibitors following the recent withdrawal of rofecoxib.

The complainant considered that the letter's primary purpose was to address questions and concerns regarding the safety of COX-2 selective inhibitors and keep healthcare providers abreast of the latest information regarding the treatment of arthritis. The complainant alleged that the letter failed to provide this information and was therefore misleading. Instead of presenting a robust discussion pertaining to all COX-2 selective inhibitors the letter only gave a précis of the Celebrex clinical data. Similarly, instead of an objective and balanced appraisal of the risks and benefits of all available treatment options for rheumatoid and osteoarthritis the letter only discussed Celebrex and in doing so failed to provide an accurate, balanced and informative safety update consistent with its stated intent.

The complainant stated that if the letter was to help health professionals make informed prescribing decisions then why did it not provide relevant information about valdecoxib, another Pfizer product? This omission was misleading and invited the reader to assume that there were currently no safety issues pertaining to valdecoxib which was not so as shown by recent criticisms by an advisory committee of the US Food and Drugs Administration (FDA).

Pfizer continued to market Celebrex as a COX-2 selective inhibitor, capable of efficacy without serious toxicity. The complainant was surprised that the letter also referred to data from the CLASS study despite that study having been discredited, doubts cast on the selectivity of celecoxib and that studies such as CLASS emphasised the gastrointestinal toxicity profile while largely ignoring other adverse events such as cardiovascular events.

The gravitas of a letter signed by the medical director and the positive impression that this could create could not be overstated. Given the seriousness of the issues surrounding COX-2s and the potential impact of this letter on continued patient safety and prescriber confidence, Pfizer's medical director should have objectively discussed the safety profile of Celebrex and valdecoxib and accurately addressed the stated intent of the mailing in a non-promotional manner.

The complainant alleged that this letter was yet another example of how companies such as Pfizer continued to bring the UK pharmaceutical industry into disrepute.

The Panel noted Pfizer's submission that the letter was sent pursuant to the withdrawal of Vioxx, primarily to reassure prescribers that Celebrex continued to be available and had an acceptable benefit-risk ratio. The first paragraph referred to the company's commitment to keeping health professionals abreast of the latest information regarding the treatment of arthritis. Reference was made to questions and concerns regarding the safety of COX-2 selective inhibitors which had arisen after the withdrawal of Vioxx. The concluding sentence of the first paragraph read 'The cardiovascular safety of Celebrex (celecoxib) is well established in long-

term studies'. The second paragraph stated that the new clinical data that prompted the withdrawal of Vioxx related specifically to that product and could not be generalised to other COX-2 selective inhibitors. Key conclusions from Celebrex clinical and epidemiology studies were then summarised in five bullet points.

The Panel considered that, in the absence of a heading to the letter, the first paragraph set the tone of the letter. In the opinion of the Panel the first paragraph made it sufficiently clear that the letter at issue was promotional material for Celebrex. Whilst the first sentence stated that the company was committed to providing the latest information on the treatment of arthritis the subsequent sentences made clear what information would be provided in the letter. The Panel did not consider that the letter was misleading as alleged because it only discussed data on Celebrex; the Panel did not consider that the discussion of such data was inconsistent with the stated intention of the letter as expressed in the introductory paragraph. No breach of the Code was ruled on this point.

This ruling was appealed by the complainant whereupon the Appeal Board noted that the introductory paragraph referred to '… questions and concerns regarding the safety of COX-2 selective inhibitors' (emphasis added) and ended with the statement 'The cardiovascular safety profile of Celebrex (celecoxib) is well established in long term studies'. However, the first sentence of the second paragraph then referred, once again, to '… COX-2 selective inhibitors' (emphasis added) in general. The Appeal Board considered that although the order of sentences in the first two paragraphs of the letter was unhelpful, the first paragraph made it sufficiently clear that the letter was promotional material for Celebrex. The Appeal Board did not consider that the letter was misleading as alleged because it only discussed data on Celebrex or that the discussion of such data was inconsistent with the stated intent of the letter as expressed in the introductory paragraph. The Appeal Board upheld the Panel's ruling of no breach of the Code.

In relation to the allegation that the omission of data on Bextra was misleading the Panel noted Pfizer's submission that this was due to ongoing discussions with regulators; it was not an attempt to imply a positive or negative cardiovascular safety profile for the product. The Panel noted its comments above about the introductory paragraph and given its view that that paragraph made it sufficiently clear that the letter was promotional material for Celebrex the Panel did not consider that the failure to discuss data on Bextra was misleading as alleged. No breach of the Code was ruled. Upon appeal by the complainant the Appeal Board considered that, despite ongoing discussions with the regulators, it would have been possible to include data on Bextra but nonetheless, on balance, it upheld the Panel's ruling of no breach of the Code.

The Panel noted that the third bullet point in the letter read 'A pooled analysis of 30,000 patients who completed arthritis trials (including CLASS) supports that Celebrex did not increase the incidence of thromboembolic events vs placebo and traditional NSAIDs'. The fourth bullet point read 'In CLASS, a long-term (12 month) prospective study, Celebrex, even at 2 to 4 times the approved doses was not associated with an increased risk of serious CV events such as heart attack, stroke or unstable angina compared to non-selective NSAIDs'. The third and fourth bullet points were respectively referenced to White *et al* (2003) and White *et al* (2002).

White *et al* (2003) had examined the rate of cardiovascular thrombotic events of Celebrex by analysing the Celebrex database from all completed clinical arthritis trials of more than four weeks' duration including 13 new medicine application studies and two large post-marketing studies, (including CLASS and SUCCESS). The analysis showed no significant increase in CV events (myocardial infarction, stroke, or death) when celecoxib-treated patients were compared with those receiving nonselective NSAIDs or placebo. The authors acknowledged that the event rates differed from those reported in recent evaluations from the CLASS trial. These differences were attributed to study design features including differences in the adjudication process, which would be expected to add to the credibility of their results. The study authors noted, as a potential study limitation, that the studies analysed were not originally designed to assess relative effects of celecoxib on CV events and so unintentional selection bias might have confounded their results. Baseline demographics including CV risk factors and use of aspirin were comparable between treatment groups. Another potential concern was that sample size, event numbers and patient-years of follow-up for the placebo and naproxen groups were relatively small and thus description of absolute risk relative to placebo must be interpreted with caution. Thus although the most confident interpretation of these data related to comparison with NSAIDs, the total number of events included in this study was relatively modest, and occurred primarily in trials geared toward the development of a database for drug approval and gastrointestinal safety assessment. Thus the power to detect true relative risks in the 1.2 to 1.4 range associated with harm was not high. This potential deficit was compensated in part by the availability and use of original source data for CV events which would be expected to add to the credibility of the results.

The Panel noted that White *et al* (2002) analysed the CLASS study. The Panel noted the company's published response to the critical Juni *et al* (2002) editorial on the CLASS study. The Panel did not have a copy of the CLASS study before it.

The Panel noted that the published criticisms on the CLASS study related to the analyses of the gastrointestinal data, not the subsequent analyses undertaken by White *et al* who had access to the original source data for CV events. The Panel noted that the citations for White *et al* (2002) and (2003) appeared prominently alongside the fourth and third bullet points respectively. The Panel did not consider that the references to the CLASS study

were misleading due to the published critical comment or because CLASS examined celecoxib's gastrointestinal safety profile as alleged; no breach of the Code was ruled.

The Panel noted that the introductory paragraph to the letter in question read 'The cardiovascular safety of Celebrex is well established in long-term studies'. The next paragraph disassociated Celebrex from the clinical data which prompted the withdrawal of Vioxx. After assessing the clinical data the penultimate paragraph read '…there is a substantial body of evidence supporting the CV safety, GI safety and efficacy of Celebrex. This distinct profile should assure you of the benefits of Celebrex'.

The Panel noted that Celebrex was contraindicated in patients with severe congestive heart failure (ref summary of product characteristics (SPC)). With regard to special precautions and warnings for use, Section 4.4 of the SPC noted that COX-2 selective inhibitors were not a substitute for aspirin for prophylaxis of cardiovascular thrombo-embolic diseases. Prescribers were urged to exercise caution if using Celecoxib in patients with a history of ischaemic heart disease. Fluid retention and oedema had been observed in patients taking Celebrex and therefore caution was urged in patients with a history of cardiac failure, left ventricular dysfunction or hypertension and in patients with pre-existing oedema from any other reason.

The Panel noted the caution expressed in the SPC and was extremely concerned that the third bullet point implied that the cardiovascular profile of Celebrex was comparable to placebo. The third bullet point did not reflect the reservations expressed by White *et al* (2003). Overall the Panel considered that the letter implied that there was no need to be concerned about the cardiovascular profile of Celebrex and that was not so. The fact that the letter was signed by the medical director reinforced this impression. The letter was misleading in this regard and incapable of substantiation; breaches of the Code were ruled. High standards had not been maintained; a breach of the Code was ruled. On balance, the Panel did not consider that the letter 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 ruled. This ruling was appealed by the complainant whereupon the Appeal Board noted that the letter was sent at a time when there were major concerns regarding the cardiovascular safety of COX-2 inhibitors. The letter was signed by Pfizer's medical director and as such would have a significant impact upon recipients who would view its content as having some standing. The Panel, however, had considered that statements in the letter were misleading with regard to the cardiovascular profile of Celebrex and could not be substantiated. Breaches of the Code were ruled which were not appealed by Pfizer. The Appeal Board considered that the letter was such that patient safety in relation to the use of Celebrex could be compromised and in that regard it brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 of the Code was ruled.

A general practitioner complained about a 'Dear Healthcare Professional' letter (ref CEL 1249) about Celebrex (celecoxib) issued by Pfizer Limited. The letter was signed by the medical director.

Celebrex was a selective cyclo-oxygenase-2 (COX-2) inhibitor indicated for symptomatic relief in the treatment of osteoarthritis (OA) or rheumatoid arthritis (RA).

COMPLAINT

The complainant stated that the letter could only be regarded as a cynical exercise aimed at promoting Celebrex in guise of a safety update on COX-2 selective inhibitors following the recent withdrawal of rofecoxib. The complainant considered that, the letter's primary purpose was to address the following points: questions and concerns regarding the safety of COX-2 selective inhibitors, and keeping healthcare providers abreast of the latest information regarding the treatment of arthritis. The complainant alleged that the letter failed to provide this information and was therefore misleading.

With regard to the questions and concerns about the safety of COX-2 selective inhibitors, one would expect to see a robust discussion addressing many of the questions and concerns pertaining to the entire COX-2 selective inhibitor class and not a précis of the clinical data supporting Celebrex. Similarly, with regard to the latest information on the treatment of arthritis, one would anticipate seeing an objective and balanced appraisal of the risks and benefits of all available options for the treatment of rheumatoid and osteoarthritis. Unfortunately, the letter only discussed Celebrex and in doing so it failed to provide an accurate, balanced and informative safety update consistent with the stated intent of the mailing.

The complainant stated that if, indeed the letter was aimed at helping health professionals make informed prescribing decisions then why did it not provide relevant safety information regarding valdecoxib, which was also promoted in the UK by Pfizer? This omission was misleading and invited the reader to assume that there were currently no safety issues pertaining to valdecoxib. The latter was clearly not the case; the US Food and Drugs Administration's (FDA) data safety and risk management advisory committee had recently criticised Pfizer for delaying announcing negative data about valdecoxib and the company's ambiguity regarding this issue. Pfizer initially defended valdecoxib, saying that it was safe in patients with rheumatoid arthritis and osteoarthritis but later qualified this position by reporting that in two trials of cardiac surgery, patients taking valdecoxib had a higher risk of stroke, heart attacks and deaths. This report also indicated that Pfizer had updated its warning that valdecoxib could cause a rare but sometimes fatal skin disorder, Stevens-Johnson syndrome, and to note that cases of the condition were being seen more often with valdecoxib than with other medicines in the same class; this warning was not included in the prescribing information in current Bextra advertisements. The latter clearly demonstrated why valdecoxib safety information was very relevant to

UK prescribers and should have been included in the letter.

Pfizer continued to market Celebrex as a COX-2 selective inhibitor, capable of efficacy without serious toxicity and continued to promote it on the basis of the CLASS study. The complainant was surprised that this letter also referred to the CLASS data despite the fact that the study had been discredited, doubts had been cast on the selectivity of celecoxib and that studies such as this gave remarkable emphasis to the gastrointestinal toxicity profile while largely ignoring other adverse events such as cardiovascular events.

The gravitas of a personal communication from the medical director and the positive impression that this could create amongst health professionals could not be overstated. Given the seriousness of the issues surrounding this particular class of medicines and the potential impact of this letter on continued patient safety and prescriber confidence, it would have behoved the Pfizer medical director to discuss objectively the safety profile of both Celebrex and valdecoxib, accurately address the stated intent of the mailing and to do so in a non-promotional manner.

The complainant alleged that this letter was yet another example of how companies such as Pfizer continued to bring the UK pharmaceutical industry into disrepute.

When writing to Pfizer the Authority asked it to respond in relation to Clauses 2, 7.2, 7.4, 7.9 and 9.1 of the Code.

RESPONSE

Pfizer apologised for any inconvenience caused and very much regretted the annoyance felt by the complainant.

Pfizer stated that the letter in question addressed specific concerns about Celebrex that were raised by health professionals (and patients alike) as a result of the withdrawal of Vioxx (rofecoxib), on 30 September 2004. This was reflected by a 16-fold increase in the number of enquiries received from health providers about Celebrex by the medical information department at Pfizer between 29 September and 1 October 2004.

The letter contained data about the safety profile of Celebrex and Pfizer submitted that this information was particularly relevant in the light of the circumstances and the level of attention COX-2s were receiving in the health and lay press, and the subsequent confusion this was causing amongst doctors and patients. There were numerous accounts of patients seeking advice from their health providers following the precipitate withdrawal of Vioxx. Most practitioners with whom Pfizer had spoken heard of this withdrawal through the lay media. Many patients who consulted their prescribers, as a result of the news, did not appear to understand if their medicine was likely to be affected. This was regardless of whether they were taking rofecoxib or Celebrex.

The situation with regard to the safety of Vioxx had become absolutely clear but Pfizer believed that there was less clarity in the perception of Celebrex, both with patients and prescribers alike. This was in spite of the clear comments in the Committee on Safety of Medicines (CSM) release that the withdrawal of rofecoxib and the issues raised thereby could not be generalised to other COX-2 selective medicines.

Pfizer's letter, therefore, was sent in response to this situation and primarily to reassure prescribers that Celebrex continued to be available and continued to have an acceptable benefit-risk ratio and that extensive data, already in the public domain, supported this position. Pfizer did not consider that the letter was misleading. It was only permitted to discuss the detail of its own products and in this case did not mention Bextra (valdecoxib) due to ongoing licensing discussions about it with the European Medicines Evaluation Agency (EMEA). Once these discussions had progressed Pfizer would be able to assess what further information health practitioners needed about Bextra and how to tell them.

Pfizer did not consider that the letter or the way in which it was introduced was misleading; all claims were substantiated and all uses of the word 'safe' or 'safety' were clearly qualified. The letter, together with the circumstances under which it was issued, contributed to the high standard with which Pfizer had responded to the real needs of health practitioners and their patients in the light of events over which it had had no control.

Pfizer considered that the complainant was wrong in his interpretation of the letter; all of the criticisms were based on interpretations of selective parts of the letter, which had been taken out of context.

The first paragraph of the letter read:

'Pfizer is committed to keeping healthcare providers abreast of the latest information regarding the treatment of arthritis. Merck's recent voluntary withdrawal of Vioxx (rofecoxib) from the market is likely to have raised questions and concerns regarding the safety of COX-2 selective inhibitors. The cardiovascular safety of CELEBREX (celecoxib) is well established in long-term studies.'

The first two sentences of this paragraph were clear and were a matter of fact. They provided the background to the letter and Pfizer did not consider any of this wording or the paragraph as a whole suggested that the primary purpose of the letter was to address 'Questions and concerns regarding the safety of COX-2 selective inhibitors', and 'Keeping healthcare providers abreast of the latest information regarding the treatment of arthritis' as alleged.

Pfizer believed that it had not made the claims stated by the complainant and that the following criticisms, also made by the complainant, were totally unfounded, namely that:

- Pfizer did not talk about the entire COX-2 class,
- Pfizer did not give a balanced appraisal of all treatment options for arthritis, and
- Pfizer did not give an accurate, balanced and informative safety update.

Pfizer stated that its medical department prepared the letter to reassure health practitioners that the

withdrawal of Vioxx did not affect Celebrex and to reinforce its cardiovascular safety profile. As stated above, Bextra data was not included due to ongoing discussions with regulatory authorities and was not an attempt to imply a positive or negative cardiovascular safety profile about the product.

Pfizer noted that the FDA had not issued the critical statements as stated by the complainant and that Pfizer was continuously in discussion with regulatory authorities to ensure that the summary of product characteristics (SPC) accurately reflected current data. The statements attributed to the FDA were in fact from a BMJ news article which was allegedly based on an interview with someone who was, at that time and prior to his recent dismissal, a member of the relevant FDA committee. Pfizer's position that valdecoxib had no increased cardiovascular (CV) risk in OA and RA patients, when compared to NSAIDs had not changed and was based on numerous data, which had been presented in a recent meta-analysis of prospective trials in OA and RA by White *et al* (2004). The FDA had not issued any official statement in which it criticised Pfizer or any of its products in this context.

The Bextra SPC already included warnings about CV adverse events, which were based on the first coronary artery bypass graft surgery (CABG) study and about severe cutaneous adverse reactions (SCARS), based on periodic safety update reviews. Both these inclusions reflected ongoing discussions between Pfizer and the EMEA. In addition, the recent CABG study had also been passed to the EMEA for consideration and eventual inclusion in the SPC. Therefore, the criticisms (which seemed to be based on only the US journalist's interview with the ex-employee of the US FDA as described above) were not true nor were they relevant to the UK situation or more widely in the EU. Therefore, all information, which could have reasonably been provided to UK prescribers, was already contained within the SPC for Bextra.

The assertion that the CLASS trial had been discredited was based on an editorial by Juni *et al* (2002), which Pfizer believed to be flawed, and, as far as this response was concerned, irrelevant. However, Pfizer provided its response to Juni *et al* for information.

In stating that the CLASS study had been discredited, the complainant had expressed a personal opinion, one that Pfizer did not share and one that was not supported by the facts. Moreover, the complainant had misinterpreted the reference to the CLASS study in the letter. Pfizer's letter referred to an analysis of the CLASS data for CV adverse events by White *et al* (2002). This study looked at CV outcomes and showed no difference between celecoxib and NSAIDs. Based on the suggested misunderstanding and what the letter actually said, Pfizer did not consider that there was any criticism to address.

Due to the impact of Vioxx's withdrawal and the level of confusion and concern amongst health professionals and patients Pfizer considered that it had a responsibility to emphasise relevant data on Celebrex (the most widely prescribed COX-2) and to confirm its continued availability. Pfizer maintained that the letter at issue provided such data in an objective manner. The company very much regretted that the complainant considered that it had acted in a disreputable manner; Pfizer believed that it acted responsibly and in the interests of health providers and their patients.

Pfizer considered that the information in the letter was accurate, balanced, fair, objective, unambiguous and reflected the evidence and was not misleading and therefore, was not in breach of Clause 7.2. All the information given in the letter could be substantiated and therefore, Pfizer could not be in breach of Clause 7.4. Pfizer had given a fair account of the CV safety profile of Celebrex and therefore was not in breach of Clause 7.9.

With regard to Clause 9.1, Pfizer considered that it had maintained high standards. The letter was a fair summary of the clinical situation with regard to Celebrex and was intended to inform practitioners so they could better manage their patients. Therefore Pfizer did not consider it was in breach of this clause.

In the light of the above Pfizer did not consider that the letter brought discredit to, or reduced confidence in, the pharmaceutical industry.

PANEL RULING

The Panel noted Pfizer's submission that the letter was sent in response to the situation which had arisen pursuant to the withdrawal of Vioxx and primarily to reassure prescribers that Celebrex continued to be available and continued to have an acceptable benefit-risk ratio. The first paragraph referred to the company's commitment to keeping health professionals abreast of the latest information regarding the treatment of arthritis. Reference was made to questions and concerns regarding the safety of COX-2 selective inhibitors which had arisen further to the withdrawal of Vioxx. The concluding sentence of the first paragraph read 'The cardiovascular safety of Celebrex (celecoxib) is well established in long-term studies'. The second paragraph stated that the new clinical data that prompted the withdrawal of Vioxx related specifically to that product and could not be generalised to other COX-2 selective inhibitors as stated in the CSM communication. Key conclusions from Celebrex clinical and epidemiology studies were then summarised in five bullet points.

The Panel considered that, in the absence of a heading to the letter, the first paragraph set the tone of the letter. In the opinion of the Panel the first paragraph made it sufficiently clear that the letter at issue was promotional material for Celebrex. Whilst the first sentence stated that the company was committed to providing the latest information on the treatment of arthritis the subsequent sentences made clear what information would be provided in the letter. The Panel did not consider that the letter was misleading as alleged because it only discussed data on Celebrex; the Panel did not consider that the discussion of such data was inconsistent with the stated intention of the letter as expressed in the introductory paragraph. No breach of Clause 7.2 was ruled on this point. This ruling was appealed.

In relation to the allegation that the omission of data on Bextra was misleading the Panel noted Pfizer's submission that this was due to ongoing discussions with regulators; it was not an attempt to imply a positive or negative cardiovascular safety profile for this medicine. The Panel noted its comments above about the introductory paragraph which set the tone for the letter and the context within which the subsequent paragraphs would be considered. Given the Panel's view that the introductory paragraph made it sufficiently clear that the letter was promotional material for Celebrex the Panel did not consider that the failure to discuss data on Bextra was misleading as alleged. No breach of Clause 7.2 was ruled. This ruling was appealed.

The Panel noted that the third bullet point in the letter in question read 'A pooled analysis of 30,000 patients who completed arthritis trials (including CLASS) supports that Celebrex did not increase the incidence of thromboembolic events vs placebo and traditional NSAIDs'. The fourth bullet point read 'In CLASS, a long-term (12 month) prospective study, Celebrex, even at 2 to 4 times the approved doses was not associated with an increased risk of serious CV events such as heart attack, stroke or unstable angina compared to non-selective NSAIDs'. The third and fourth bullet points were respectively referenced to White *et al* (2003) and White *et al* (2002).

The Panel noted that White *et al* (2003) examined the rate of cardiovascular thrombotic events of Celebrex by analysing the Celebrex database from all completed clinical arthritis trials of more than four weeks in duration including 13 new medicine application studies and two large post-marketing studies, (including CLASS and SUCCESS). The authors noted that their analysis showed no significant increase in CV events (myocardial infarction, stroke, or death) when patients treated with celecoxib were compared with patients receiving nonselective NSAIDs or placebo. The authors acknowledged that the event rates differed from those reported in recent evaluations from the CLASS trial. These differences were attributed to study design features including differences in the adjudication process, which would be expected to add to the credibility of their results. The study authors noted, as a potential study limitation, that 'the studies utilized for analysis were not originally designed to assess relative effects of celecoxib on cardiovascular events. Thus unintentional selection bias may have confounded our results'. Baseline demographics including CV risk factors and use of aspirin were comparable between treatment groups. Another potential concern was that sample size, event numbers and patient-years of follow-up for the placebo and naproxen groups were relatively small and thus description of absolute risk relative to placebo must be interpreted with caution. 'Thus although the most confident interpretation of these data relates to comparison with NSAIDs, the total number of events included in this study is relatively modest, and occurred primarily in trials geared toward the development of a database for drug approval and gastrointestinal safety assessment. Thus the power to detect true relative risks in the 1.2 to 1.4 range associated with harm is not high'. This potential deficit was compensated in part by the availability and use of original source data for CV events which would be expected to add to the credibility of the results.

The Panel noted that White *et al* (2002) analysed the CLASS study. The Panel noted the company's published response to the critical Juni *et al* editorial on the CLASS study. The Panel did not have a copy of the CLASS study before it.

The Panel noted that the published critical comment on the CLASS study related to the analyses of the gastrointestinal data. It did not relate to the subsequent analyses undertaken by White *et al* who had access to the original source data for CV events. The Panel noted that the citations for White *et al* (2002) and (2003) appeared prominently alongside the fourth and third bullet points respectively. The Panel did not consider that the references to the CLASS study were misleading due to the published critical comment or because CLASS examined celecoxib's gastrointestinal safety profile as alleged; no breach of Clause 7.2 was ruled.

The Panel noted that the introductory paragraph to the letter in question read 'The cardiovascular safety of Celebrex is well established in long-term studies'. The next paragraph disassociated Celebrex from the clinical data which prompted the withdrawal of Vioxx. After assessing the clinical data the penultimate paragraph read '…there is a substantial body of evidence supporting the CV safety, GI safety and efficacy of Celebrex. This distinct profile should assure you of the benefits of Celebrex'.

The Panel noted the Celebrex SPC stated that the product was contraindicated in patients with severe congestive heart failure. With regard to special precautions and warnings for use, Section 4.4 of the SPC noted that COX-2 selective inhibitors were not a substitute for aspirin for prophylaxis of cardiovascular thrombo-embolic diseases. Prescribers were urged to exercise caution if using Celecoxib in patients with a history of ischaemic heart disease. As with other medicines known to inhibit prostaglandin synthesis fluid retention, and oedema had been observed in patients taking Celebrex and therefore caution was urged in patients with a history of cardiac failure, left ventricular dysfunction or hypertension and in patients with pre-existing oedema from any other reason.

The Panel noted the caution expressed in the SPC. The Panel was extremely concerned that the third bullet point gave the impression that the cardiovascular profile of Celebrex was comparable to placebo. The third bullet point did not reflect the reservations expressed by White *et al*. Overall the Panel considered that the letter at issue gave the impression that readers need not be concerned about the cardiovascular profile of Celebrex and that was not so. The fact that the letter was signed by the medical director reinforced this impression. The letter was misleading in this regard and incapable of substantiation; breaches of Clauses 7.2, 7.4 and 7.9 were ruled. High standards had not been maintained; a breach of Clause 9.1 was ruled.

On balance, the Panel did not consider that the letter warranted a ruling of a breach of Clause 2 which was

reserved as a sign of particular censure; no breach of Clause 2 was ruled. This ruling was appealed.

APPEAL BY COMPLAINANT

The complainant appealed the Panel's rulings that there was no breach of Clause 7.2 in respect of the following:

- that the Panel did not consider that the letter was misleading because it only discussed data on celecoxib and that the discussion of such data was not inconsistent with the stated intention of the letter as expressed in the introductory paragraph.
- that the Panel did not consider that failure to discuss data on valdecoxib was misleading.

The complainant also appealed the Panel's ruling that the letter did not warrant a ruling of a breach of Clause 2.

The complainant noted that the first paragraph of the letter did not explicitly state that the purpose of the letter was to support the promotion of only celecoxib; even the Panel noted the absence of a heading to the letter or a clear statement of intent. From the readers' perspective the wording of the first paragraph set the tone in respect of the safety concerns regarding rofecoxib and how this situation related to the COX-2 selective inhibitors as a class. Given the latter, it was unlikely that readers would surmise that the stated intent of the letter was to focus only on the promotion of celecoxib; this only became apparent after the first two paragraphs. Further, it was inappropriate to expect readers to guess whether information was promotional or non-promotional, particularly when it purported to be a medical communication on a matter of great importance from a medical director.

Indeed, if the stated intent of the letter was to address questions and concerns regarding 'COX-2 selective inhibitors' (emphasis added) then, as a minimum, it would be reasonable for readers to expect to be provided with safety information relating to the two medicines in this class which were actively promoted by Pfizer ie celecoxib and valdecoxib. In the absence of an explicit heading or statement, the first paragraph of the letter did not provide the reader with any indication of what was to follow and therefore misled by omission.

In its response, Pfizer had stated that the letter 'addressed specific concerns about Celebrex that were raised by health professionals (and patients alike)' and that 'this information was particularly relevant in the light of the circumstances and the level of attention COX-2s were receiving in the health and lay press, and the subsequent confusion this was causing amongst doctors and patients'. Pfizer had also stated, 'Many patients who consulted their prescribers, as a result of the news, did not appear to understand if their medicine was likely to be affected. This was regardless of whether they were taking rofecoxib or Celebrex'. Pfizer had further stated that 'The situation with regard to the safety of Vioxx had become absolutely clear and that there was less clarity in the perception of Celebrex, both with patients and prescribers alike'. The complainant noted that this reported lack of understanding amongst patients appeared only to be limited to those patients taking rofecoxib or celecoxib; one could only presume that those patients and doctors using valdecoxib were neither confused nor concerned following the worldwide withdrawal of rofecoxib. On this basis the complainant imagined that Pfizer would not have received any enquiries regarding the CV safety of valdecoxib.

The complainant noted Pfizer's contention that the letter did not consider valdecoxib due to ongoing licensing discussions with the EMEA. Did these discussions involve the CV safety concerns regarding valdecoxib? Interestingly Pfizer appeared to be able to consider celecoxib despite ongoing discussions with European and national regulatory authorities such as in Turkey; why was there inconsistency regarding valdecoxib? Another inconsistency related to the invitation to contact Pfizer medical information 'If you require any further information on Pfizer COX-2 selective inhibitors'. The complainant questioned what written information could this department provide that could not be provided in a letter addressed to health professionals especially when Pfizer was in discussion with the EMEA? So whilst Pfizer was engaged in discussions with the EMEA precisely what information was being provided to patients and prescribers who might have genuine and serious concerns about the CV safety of valdecoxib; presumably none if this could not be discussed in any written communication such as this letter? Maybe the invitation to contact the medical information department only related to enquires regarding valdecoxib that were not related to concerns regarding its CV safety? The complainant stated that perhaps he was mistaken and despite the extensive publicity in the health and lay press the issue of 'clarity of perception by patients and prescribers' described by Pfizer only affected celecoxib and not those using valdecoxib. Such woolly argumentation for not including relevant information about valdecoxib was scandalous.

In the complainant's opinion Pfizer's rationale for generating the letter could, and should have, equally applied to valdecoxib. Thus the omission of any information in the letter regarding valdecoxib only led the reader to assume that the confusion and concerns described by Pfizer related solely to celecoxib and that both patients and doctors using valdecoxib need not worry about any safety concerns, CV or otherwise. This was clearly not so and the absence of any information regarding valdecoxib, whatever the reason, misled by omission, misinformed and generated more doubts, concerns and questions.

The complainant noted that Pfizer further supported its decision not to provide updated information on valdecoxib on the basis that all of the information that could have been reasonably provided to UK prescribers was already in the SPC. How did Pfizer's medical director think the reader was going to come to this conclusion given the intensity of the ongoing public debate regarding this matter especially if a statement to this effect was not in the letter? In fact, the ongoing debate regarding celecoxib was exactly analogous to that affecting valdecoxib. So why did Pfizer deem it appropriate to address the celecoxib

issue via a letter promoting the safety profile of celecoxib and not simply state that all of the information which could be reasonably provided was already contained in the SPC?

The complainant noted that Pfizer stated that his criticisms about the CV concerns regarding valdecoxib were not true and irrelevant to the UK. Pfizer's response in this regard was patronising and failed to recognise that valdecoxib was currently associated with a black triangle in the UK, which clearly indicated that the medicine was subject to heightened pharmacovigilance and adverse event reporting procedures. Therefore any safety concerns or ongoing debates regarding this medicine were very relevant to the situation in the UK and needed to be recognised and addressed by Pfizer.

The complainant noted that NHS prescribing advisers had recently told GPs not to switch patients who were taking rofecoxib to COX-2 selective inhibitors, which included celecoxib and valdecoxib. The National Prescribing Centre reviewed data on COX-2 selective inhibitors and found clear evidence that they had no gastrointestinal benefits over NSAIDs and increasing evidence of CV risks. The latter information was made available to GPs via the MeReC Extra bulletin, which was funded by the National Institute for Clinical Excellence (NICE). The complainant noted that his concerns regarding this letter were being investigated by the Medicines and Healthcare products Regulatory Agency (MHRA) which was currently reviewing new data based on a meta-analysis presented on 10 November 2004 at the American Heart Association by Fitzgerald. This analysis pooled data from the two studies of patients who underwent CABG procedures (n=2098) and another meta-analysis of randomized controlled trials of valdecoxib in arthritis patients (n=5673). Of those, 5930 patients were randomized to valdecoxib and 1841 to placebo. Among bypass patients taking valdecoxib, 31 had myocardial infarctions (MIs) or strokes, compared to five MIs and strokes in the placebo arm. Among the arthritis patients, there were 14 MIs and strokes in the valdecoxib arm and two in the placebo arm. When the data were pooled, the risk of MIs and strokes was more than twice as high in the valdecoxib arm, compared with the placebo arm. Specifically, the relative risk was 2.19, with a confidence interval of 1.19-4.03 and a p-value of 0.01 for patients taking valdecoxib and 1.77 for those prescribed the medicine for arthritis.

Notwithstanding the latter, in its response Pfizer cited an analysis that included nearly 8000 patients treated with valdecoxib for 6 to 52 weeks. Pfizer contended that these data showed that short-term and intermediate-term treatment with valdecoxib was not associated with an increased incidence of thrombotic events relative to non-selective NSAIDs or placebo in osteoarthritis and rheumatoid arthritis patients (White *et al* 2004). However, Pfizer failed to acknowledge the authors' comments that 'studies used in this meta-analysis were not originally designed to assess relative effects of valdecoxib on cardiovascular events' and that 'unintentional selection bias may have confounded our results'. The authors also stated that 'the most confident interpretation of these data relates to the comparison with NSAID' and that 'the total number of events included in this study is relatively modest and occurred primarily in trials geared towards the development of a database for drug approval and general safety assessment'. In other words these particular data did not necessarily reflect the situation that might exist in clinical practice.

The stated aim of the letter was to provide an update on COX-2 selective inhibitors. The above points regarding the CV concerns surrounding valdecoxib were only some of many which, most recently, included the correspondence to the New England Journal of Medicine from three eminent physicians, two of whom had worked in collaboration with Pfizer (Ray *et al* 2004). Despite this volume of public concern regarding valdecoxib the letter failed to provide any information about it and, given its stated intent, the letter could therefore be described as unbalanced and misleading. Pfizer's explanation for the omission of valdecoxib information was woefully inadequate. Doctors needed to be made aware of all information regarding valdecoxib in order to correctly assess the risk-benefit profile of these medicines and advise patients appropriately. To provide such information in an incomplete and selective manner solely at the discretion of the manufacturer, as evidenced by the letter, suggested that ensuring prescribers' confidence and patient safety were not necessarily the foremost concern of Pfizer or its medical director.

By its own admission Pfizer acknowledged that this particular safety issue affected the COX-2 selective inhibitors class as a whole which therefore also included valdecoxib. Therefore it seemed odd that a letter from the medical director should focus only on promoting celecoxib. Maybe this was because there were no patients taking valdecoxib and that the Pfizer medical information department had not received any calls from concerned doctors and patients regarding valdecoxib. Maybe the mailing focussed on celecoxib simply as a matter of expediency in which the relatively fewer patients and doctors using valdecoxib compared to those using celecoxib were simply not a commercial priority. The commercial priority supported by this letter was to maximise the opportunity to switch patients from rofecoxib to celecoxib. When backed up by the medical director the provision of the updated risk-benefit argument supporting celecoxib was likely to be more compelling to doctors as was the omission of valdecoxib information. In fact, from a commercial perspective the provision of any information on valdecoxib would only detract from celecoxib and raise further questions suggesting to readers that maybe the adverse CV profile of COX-2 selective inhibitors was a class effect.

The complainant asked whether this was an example where the boundary between commercial and professional priorities had become unrecognisable and that a serious safety issue had been hijacked with the complicity of the medical director as a commercial opportunity. Indeed if one were to accept the latter and the argument that the letter clearly promoted celecoxib then why did it not carry the celecoxib branding to immediately alert the reader as to its

nature and why was it not signed by a product or marketing manager? The stated intent and medical director's signature made it difficult for the reader to judge immediately if the letter was promotional or a genuine medical communication from one peer to another regarding an important matter of safety.

In summary, the letter selectively promoted a product of greater commercial significance in preference to another medicine of the same class, both of which were marketed by Pfizer. The focus on celecoxib and omission of valdecoxib information was unacceptable given the context and rationale for the letter ie the delivery of a safety update regarding COX-2 selective inhibitors marketed by Pfizer. If this was not the stated intent then it should have been, given the volume of concern regarding both medicines. Any reasonable doctor would want to know why this was not a reasonable expectation particularly when the letter was sent under the pretext of a medical communication from the medical director on this very subject. At the heart of this complaint was the fundamental concern that the letter appeared to focus on a medicine of commercial importance to Pfizer whilst completely ignoring the very relevant and genuine need for information regarding valdecoxib. Provision of the latter was expected given the context of the letter and its provision would have enabled doctors to make a proper assessment of the risk-benefit associated with this medicine and allay the concerns of patients using it. The complainant considered that this brought the pharmaceutical industry into disrepute.

COMMENTS FROM PFIZER

Pfizer stated that the aim of the letter was clear: it was a promotional piece designed to communicate the continued availability of Celebrex based on an acceptable benefit-risk profile. The reasons for only providing information on Celebrex were:

- In the absence of new data concerning the risk benefit profile of celecoxib, Pfizer wished to communicate the data relevant to its continued availability.
- New data had warranted discussions with the EMEA regarding the SPC for Bextra, which was authorised under the EU's centralised procedure. Subsequent to these discussions with the EMEA, the Bextra SPC had been updated and an urgent communication was sent to prescribers on 21 December 2004. The inclusion of Bextra information, either with the Celebrex mailing or as a separate letter, before the conclusion of the regulatory discussions, would have been irresponsible and inappropriate.

Pfizer noted the Panel's conclusion that the Celebrex letter was clear in its aims and was not misleading either in its stated objectives or in its not including information regarding Bextra. The company acknowledged, however, the Panel's finding that when taken as a whole, the letter might have been misleading with respect to the CV profile of celecoxib. Pfizer restated that it was never its intention to mislead or communicate anything other than information consistent with the SPC and the fact of the continued availability of Celebrex during a confusing time for prescribers of COX-2 selective inhibitors.

Pfizer did not accept that the recent announcements of safety data from long-term cancer prevention trials reinforced the appropriateness, or otherwise, of the Panel's rulings. The EMEA was currently carrying out a pan-European review of the CV safety of all COX-2 selective inhibitors taking into account these new data and had yet to announce its findings. At the time of the complaint, and to date, there had been no prospective or retrospective arthritis studies that had shown an increased incidence of CV adverse events with celecoxib compared with traditional NSAIDs. The very important new safety data from one long-term cancer prevention trial were being considered together with new data from a similar cancer prevention trial, a study in Alzheimer's disease and all previous data.

Pfizer denied that it had breached Clause 2 of the Code. The letter was a responsible piece of promotional material, sent to address evident concerns at a time of confusion. Such breaches of the Code as were identified by the Panel in its ruling were not such as to merit the particular censure for which Clause 2 was reserved, as found by the Panel in its ruling.

With respect to the matters set out in the appeal, Pfizer considered that it had addressed the main issues raised:

- The aim of the letter was clearly laid out in its first paragraph and therefore it was not misleading in only considering Celebrex.
- Due to ongoing discussions with the EMEA about the Bextra SPC, it was not appropriate to send out information on this medicine before the conclusion of these discussions. A safety update letter had now been sent communicating these SPC changes.

Pfizer noted that the complainant had stated 'Pfizer stated that my criticisms about the CV concerns regarding valdecoxib was not true and irrelevant to the UK. Pfizer's response in this regard was patronising and failed to recognise that valdecoxib was associated with a black triangle in the UK'.

Pfizer noted the complainant's original comments regarding the omission of valdecoxib data, criticisms of Pfizer by the FDA and its response on those points. Pfizer maintained that the omission of valdecoxib was not misleading nor did it suggest that there were no safety concerns pertaining to valdecoxib.

Pfizer maintained that the FDA had not criticised Pfizer in this context and that the complainant's comments, which were based on an article written by a US journalist were not necessarily true nor were they transposable to the UK. The Bextra SPC and prescribing information, which at the time of the complaint contained warnings about cardiac surgery and cutaneous reactions, had recently been updated to reflect current information on both of these safety issues.

The complainant had misquoted and misinterpreted Pfizer's response to the complaint. Pfizer took its

customers' concerns very seriously and always tried to address such concerns effectively and in a timely manner. This was true for all Pfizer medicines, including Celebrex and Bextra.

Pfizer noted that regulatory bodies around the world were reviewing all relevant data on all COX-2s. Interim guidance was available from the MHRA and definitive guidance, based on a thorough review of the data, would be available when this review was complete.

Pfizer repeated that an analysis of studies in OA and RA patients had not shown an increased risk of CV adverse events relative to NSAIDs (White *et al* (2004)). The criticisms the complainant applied to this study (made by the authors themselves), which could also have been applied to the study he mentioned in the previous paragraph, did not detract from the fact that the meta-analysis was highly relevant to the issue currently under review.

Pfizer acknowledged that many doctors and patients might have important questions and concerns about the safety of all COX-2 selective inhibitors and also about NSAIDs generally, and the company took these extremely seriously. Its priority was patient safety and its objective was to supply prescribers with timely, appropriate and accurate information on its products, according to the data it had available at any given time.

Pfizer rejected the very serious allegation that 'a serious safety issue had been hijacked with the complicity of the medical director as a commercial opportunity'. The safety of its patients was its professional and commercial priority. Pfizer firmly believed that the letter was responsible, appropriately reflected the data available at the time, and responded to the needs of prescribers.

The letter was clearly a promotional mailing and the identity of the signatory did not have an impact on this.

In summary, the Celebrex letter was clear in its aims and content and was produced to communicate the benefit-risk profile for celecoxib and its continued availability in light of the withdrawal of rofecoxib.

The Bextra SPC was under discussion with the EMEA and so it was inappropriate to provide valdecoxib information at that time. These discussions resulted in SPC changes, for which a safety update letter had been issued.

The Panel had acknowledged that the mailing did not mislead with regard to its aims or in its omission of valdecoxib information but did rule breaches of Clauses 7.2, 7.4, 7.9 and 9.1 which Pfizer had accepted.

In the light of the above and as with its original response, Pfizer stated that it had tried to maintain the highest standards and it did not believe that this letter brought discredit to, or reduced confidence in, the pharmaceutical industry. Pfizer believed that the letter did not warrant a breach of Clause 2, as found by the Panel in its original ruling.

FURTHER COMMENTS FROM COMPLAINANT

The complainant did not consider that Pfizer's comments satisfactorily addressed the points, assertions or questions outlined in the appeal. This suggested that Pfizer had no credible arguments to substantiate its decision to omit information concerning valdecoxib from the letter and were keen to continue fudging the issues.

The complainant noted that the MHRA had also investigated, and subsequently upheld, his original complaint that the letter failed to provide an accurate, balanced and informative safety update consistent with the stated intent of the letter (a copy of the MHRA's consideration was provided). Despite this, Pfizer contended that to have included valdecoxib information before discussions with the EMEA had concluded would have been irresponsible and inappropriate. Whilst laudable, this position seemed incongruous with Pfizer's acknowledgement that 'when taken as a whole the letter might have been misleading with respect to the CV profile of celecoxib'. The complainant stated that from this one could only surmise that Pfizer's perspective was that it was acceptable to be irresponsible and inappropriate about the CV safety of its number one COX-2 selective inhibitor and in doing so mislead prescribers about celecoxib; this at a time when the safety of COX-2s including celecoxib, was in question the subject of enquiry by many regulatory authorities. On the other hand Pfizer purported to being whiter-than-white when it came to not taking the opportunity to reaffirm, or otherwise, the CV safety of valdecoxib and cited ongoing discussions with the EMEA as the reason for not doing so in the letter. The complainant asked was Pfizer also not in discussion with the EMEA and other regulatory authorities, such as the Turkish regulatory authority and the MHRA, regarding celecoxib prior to the letter being sent out or was this not a consideration given the commercial importance of celecoxib to the company?

The complainant stated that surely Pfizer's acknowledgement indicated that the company hijacked a serious safety issue for commercial gain and knowingly sent out a letter that misled prescribers and inappropriately and irresponsibly promoted the as yet unproven CV safety of celecoxib.

Pfizer's response to the appeal did not allay the complainant's concerns and only strengthened his belief that the company had brought the pharmaceutical industry into disrepute. Thankfully, most of the industry representatives the complainant encountered maintained a very high and exemplary standard of professionalism. However, he had yet to encounter a more cynical and disgraceful example of commercial opportunism being proffered as medical advice at the significant cost of patient safety and prescriber confidence.

APPEAL BOARD RULING

The Appeal Board noted that the introductory paragraph of the letter referred to '… questions and concerns regarding the safety of COX-2 selective inhibitors' (emphasis added) and ended with the statement 'The cardiovascular safety profile of

Celebrex (celecoxib) is well established in long term studies'. However, the first sentence of the second paragraph then referred, once again, to '… COX-2 selective inhibitors' (emphasis added) in general. The Appeal Board considered that although the order of sentences in the first two paragraphs of the letter was unhelpful, the first paragraph made it sufficiently clear that the letter was promotional material for Celebrex. The Appeal Board did not consider that the letter was misleading as alleged because it only discussed data on Celebrex or that the discussion of such data was inconsistent with the stated intention of the letter as expressed in the introductory paragraph. The Appeal Board upheld the Panel's ruling of no breach of Clause 7.2. The appeal on this point was unsuccessful.

The Appeal Board noted Pfizer's submission that data on Bextra was not included in the letter because of ongoing discussions with regulators. The Appeal Board noted its comments above that the introductory paragraph made it sufficiently clear that the letter was promotional material for Celebrex. Whilst the Appeal Board considered it would have been possible to have included data on Bextra it did not consider, on balance, that failure to do so was misleading as alleged and upheld the Panel's ruling of no breach of Clause 7.2. The appeal on this point was unsuccessful.

The Appeal Board noted that the letter in question was sent at a time when there were major concerns regarding the cardiovascular safety of COX-2 inhibitors. The letter was signed by Pfizer's medical director and as such would have a significant impact upon recipients who would view its content as having some standing. The Panel, however, had considered that statements in the letter were misleading with regard to the cardiovascular profile of Celebrex and could not be substantiated. Breaches of the Code were ruled which were not appealed by Pfizer. The Appeal Board considered that the letter was such that patient safety in relation to the use of Celebrex could be compromised and in that regard it brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled. The appeal on this point was successful.

Complaint received **1 November 2004**

Case completed **29 March 2005**

CASE AUTH/1667/12/04

GILEAD SCIENCES v MERCK SHARP & DOHME

Cancidas 'Dear Healthcare Professional' letter

Gilead Sciences complained about a two page 'Dear Healthcare Professional' letter sent by Merck Sharp & Dohme. The letter was headed 'New England Journal of Medicine Publication Alert' and presented the results of Walsh *et al* (2004), which compared Cancidas (caspofungin) with AmBisome (liposomal amphotericin B) as empirical antifungal therapy in patients with fever and neutropenia. Gilead Sciences supplied AmBisome.

Gilead Sciences noted that although Cancidas was only licensed for the treatment of adults the letter had been sent to a number of paediatricians thus promoting an unlicensed indication.

The Panel noted that the Cancidas summary of product characteristics (SPC) stated that 'Caspofungin had not been studied in paediatric patients and use in patients under 18 years of age was not recommended. Merck Sharp & Dohme had instructed its mailing house to send the letter to, *inter alia*, hospital specialists involved in the treatment of patients with fungal disease. That list included haematologists but not paediatricians. The letter was received by a consultant paediatric haematologist. The Panel did not consider that the instructions given to the mailing house were unreasonable, given the licensed indication, or that the distribution of the letter as described amounted to the promotion of Cancidas outwith the terms of its marketing authorization or was otherwise inconsistent with its SPC. The first paragraph of the letter clearly stated that Cancidas was licensed for use in adults. No breach of the Code was ruled.

Upon appeal by Gilead the Appeal Board considered that as Cancidas was not indicated for use in patients aged under 18 years of age, Merck Sharp & Dohme should have instructed its mailing house to exclude from the mailing list all doctors whose professional address was a children's hospital. The letter had been sent to a consultant paediatric haematologist at a children's hospital. The Appeal Board considered that given the product's licensed indication, the distribution of the letter as described amounted to the promotion of Cancidas outside the terms of its marketing authorization and was inconsistent with its SPC. A breach of the Code was ruled.

Gilead Sciences alleged that the claim 'The results from this head to head trial support the use of Cancidas as first line empirical antifungal therapy instead of AmBisome 3mg/kg/day' misleadingly implied that Cancidas was shown to be more efficacious in Walsh *et al* and therefore should be used instead of AmBisome. Although the following bullet point read 'Cancidas was at least as effective as AmBisome …' the impression given was that Cancidas was better than AmBisome. Walsh *et al* showed that Cancidas was non-inferior to AmBisome and therefore a more balanced claim should position Cancidas as an alternative to, rather than a replacement for, AmBisome.

The Panel noted that Walsh *et al* examined the efficacy and safety of Cancidas compared with AmBisome for empirical antifungal therapy in patients with persistent fever and neutropenia. The primary analysis was designed to show whether the outcome in the Cancidas group was non-inferior to that in the AmBisome group. The primary efficacy endpoint was a favourable overall response as determined by a five-component endpoint. Secondary efficacy assessments consisted of assessments of each component of the primary endpoint. In relation to overall response the study authors noted that Cancidas fulfilled the statistical criteria for non-inferiority to AmBisome and concluded that Cancidas was as efficacious as AmBisome in patients with persistent fever and neutropenia and was, overall, better tolerated than AmBisome. It offered a new option for empirical antifungal therapy.

The Panel did not accept that the claim at issue implied greater efficacy for Cancidas compared with AmBisome as alleged. The claim referred to 'results' and so was likely to relate to more than one parameter. The Panel considered that the claim implied that Cancidas was an alternative first line antifungal therapy to AmBisome and noted that the following two bullet points set out the reasons why ie the two were at least as effective as each other but Cancidas was significantly better tolerated. The Panel did not consider that the claim, in the context in which it appeared, was misleading as alleged. No breach of the Code was ruled.

Gilead Sciences stated that, in clinical trials, the accepted way to determine the efficacy of an antifungal agent in empiric therapy was to use the following composite primary endpoint: successful treatment of baseline fungal infection; no breakthrough fungal infections during administration of study medicine or within 7 days of completion of treatment; survival for 7 days after completion of study therapy; no premature discontinuation of study medicine because of toxicity or lack of efficacy and resolution of fever during neutropenia. Walsh *et al* deemed a patient to have been successfully treated if they fulfilled all five components of the composite endpoint. The study was powered to show non-inferiority between Cancidas and AmBisome based on the composite endpoint.

Gilead Sciences referred to recent debate regarding the statistical significance of the differences between antifungal agents when assessment was made on the basis of each of the individual components. It was generally agreed that a stricter measure of statistical significance needed to be applied to individual components of the composite endpoints. In order to account for multiple comparisons in the analysis of subgroups, a statistical factor, the Bonferroni correction, needed to be applied. The p value for significance for each component endpoint was therefore around the order of $p \leq 0.01$ (rather than $p \leq 0.05$).

Gilead Sciences alleged that the presentation of the five components of the composite endpoints was misleading. Firstly, the five individual components as 'primary end points' in the statement 'Achievement of an overall favourable response required the patient to successfully meet all five primary end-point criteria'. Secondly, the p values for two of the components, namely, no breakthrough fungal infection and resolution of fever were described as 'ns', which Gilead Sciences took to imply 'no significance'. The p values for the other three components were stated, and all were ≤ 0.05, which implied a significant difference in favour of Cancidas in each. In intercompany correspondence, Merck Sharp & Dohme had stated that it did not consider that any statistical correction was needed when drawing conclusions regarding the components of the composite endpoint. This went against accepted statistical practice.

The Panel considered that the claim at issue 'Achievement of an overall favourable response required the patients to successfully meet all five primary end-point criteria' was ambiguous. Nowhere in the letter was it clearly stated that the primary endpoint was a composite of five criteria. The Panel ruled that the claim was misleading as alleged.

With regard to use of the Bonferroni correction the Panel noted that there appeared to be no consensus on when or if it should be applied. The Panel noted Walsh *et al* prespecified that secondary efficacy assessments would consist of assessments of each component of the primary endpoint. These were the results which were reported in the letter; results with a p value of >0.05 had been reported as non-significant. The Panel considered that given that the secondary efficacy assessments were prespecified and that the letter clearly stated the statistical significance of each one, the representation of the components of the composite endpoint was not misleading as alleged. No breach of the Code was ruled.

Upon appeal by Gilead Sciences the Appeal Board noted that Walsh *et al's* description of the statistical analysis did not state, with regard to the efficacy results, what p value represented statistical significance. (This information was given for the safety analysis). In a table of results the authors stated the p values for each of the five components of the primary endpoint but did not ascribe statistical significance to any of them. In a discussion of the components of the primary endpoints the authors stated that the 'data *suggest* (emphasis added) that caspofungin-treated patients had better outcomes than patients treated with liposomal amphotericin B with respect to three of the components'. These three components were those for which the letter gave p values of 0.05, 0.04 and 0.03 thus, in the absence of any statement to the contrary, allowing some readers to assume that statistical significance had been proven. This was compounded by the use in the letter of p=ns for the two other components. By contrast the Appeal Board noted the authors' more cautious interpretation of the results. The Appeal Board considered that the presentation of the study results was thus misleading in breach of the Code.

Gilead Sciences stated that the claim 'In addition, Cancidas demonstrated a superior tolerability profile …' could not be substantiated. The letter offered no qualification of what constituted a 'superior tolerability profile'.

The Panel noted that the claim in full read 'In addition, Cancidas demonstrated a superior tolerability profile with nephrotoxicity observed in 2.6% patients vs 11.5% with AmBisome (p<0.001)'.

Walsh *et al* concluded that fewer patients who received Cancidas sustained a nephrotoxic effect (p<0.001), an infusion-related event (p<0.001), any medicine-related adverse event (p<0.001) or discontinued therapy because of a medicine-related adverse event (p=0.04). Although the rates of medicine-related adverse events reported most frequently were similar in the two groups, several occurred less often with Cancidas than with AmBisome. The study authors concluded that Cancidas was overall, better tolerated than AmBisome. The Panel thus considered that the claim at issue could be substantiated. No breach of the Code was ruled.

Gilead Sciences alleged that the claim 'This new published data, comparing Cancidas to AmBisome, provides the definitive evidence enabling Cancidas to set a new and improved standard in antifungal empirical therapy in adult neutropenic patients' implied an efficacy advantage for Cancidas over AmBisome, which was not substantiated by Walsh *et al*. As previously discussed, the study showed *non-inferiority* of Cancidas to AmBisome. Gilead Sciences alleged that the claim was thus exaggerated, inaccurate, unbalanced and incapable of substantiation.

The Panel considered that its comments in relation to the claim 'The results from this head to head trial support the use of Cancidas as first line empirical antifungal therapy instead of AmBisome 3mg/kg/day' were relevant here. The claim would be considered in light of the letter as a whole. The Panel did not consider that the claim implied an efficacy advantage for Cancidas over AmBisome. The claim summarized the data which had already been presented ie that Cancidas was at least as effective as AmBisome but better tolerated. No breach of the Code was ruled.

Upon appeal by Gilead Sciences the Appeal Board noted that Walsh *et al* concluded that 'caspofungin was as efficacious as liposomal amphotericin B in patients with persistent fever and neutropenia and was, overall, better tolerated than liposomal amphotericin B. Thus caspofungin provides a new option for empirical antifungal therapy in these patients'. The claim at issue, however, read 'This new published data, comparing Cancidas to AmBisome, provides the definitive evidence enabling Cancidas to set a new and improved standard in antifungal empirical therapy in adult neutropenic patients'.

The Appeal Board noted Merck Sharp & Dohme's submission that the claim encompassed

considerations of efficacy, tolerability and potentially, cost. With regard to efficacy the Appeal Board noted its comments above. With regard to tolerability the Appeal Board noted that Walsh *et al* reported less nephrotoxicity in Cancidas-treated patients compared with those treated with AmBisome, and Gilead Sciences' submission that there was no data to show whether the concomitant use of nephrotoxic medicines was equal in both groups. Overall the Appeal Board considered that the claim at issue exaggerated the findings of Walsh *et al* and particularly noted in that regard the use of the phrase 'the *definitive* (emphasis added) evidence'. A breach of the Code was ruled. The Appeal Board further considered that the claim could not be substantiated and ruled a breach of the Code.

Gilead Sciences alleged that a comparison of the average daily cost for treating a 70kg patient for 14 days with Cancidas v AmBisome at 3mg/kg/day vs AmBisome 5mg/kg/day was unfair and misleading. The licensed dose of Cancidas was compared to a higher than licensed dose of AmBisome (5mg/kg/day).

The Panel considered the cost comparison misleading as alleged and ruled a breach of the Code.

Gilead Sciences Limited complained about a two page 'Dear Healthcare Professional' letter (ref 10-05 CAN.04.GB.43124.L) for Cancidas (caspofungin) sent by Merck Sharp & Dohme Limited. The letter was headed 'New England Journal of Medicine Publication Alert' and presented the results of a recently published trial, Walsh *et al* (2004), which compared Cancidas with AmBisome (liposomal amphotericin B) as empirical antifungal therapy in patients with fever and neutropenia.

1 Unlicensed promotion to paediatricians

COMPLAINT

Gilead Sciences noted that although Cancidas was only licensed for the treatment of adults the letter in question was distributed to a number of paediatricians. A reply slip addressed to a paediatrician, which was sent with the letter, was provided. The reply slip gave the recipient the opportunity to request a copy of Walsh *et al* and to schedule a visit with a sales representative. In intercompany correspondence Merck Sharp & Dohme had denied instructing its mailing house to send the letter to paediatricians but this had clearly occurred. Under the Code, companies were responsible for the activities of agents acting on their behalf. Gilead Sciences alleged that the distribution of the letter therefore constituted a clear case of promotion in an unlicensed indication in breach of Clause 3.2 of the Code.

RESPONSE

Merck Sharp & Dohme was unable to comment on how specific doctors came to receive the material as Gilead Sciences had not provided it with any information as to who these individuals were.

However, the instructions sent to the mailing house (a copy of which was provided) stated that the letter should be sent to hospital doctors with primary and secondary speciality in oncology, AIDS/HIV, haematology, microbiology, transplant, and intensive care (ie those specialists involved in the treatment of patients with fungal disease), plus hospital pharmacists. This seemed an acceptable target audience as Merck Sharp & Dohme aimed to reach any health professional to whom the publication would be of interest and relevance, and who might be involved in prescribing Cancidas according to its licensed indication in empirical therapy. There was no mention of paediatricians, however, it was very difficult to ensure that no doctors in that list would have a special interest in treating children.

If Merck Sharp & Dohme knew which paediatricians had received this letter (or indeed other specialists who treated only children), it would ensure they were not sent any future promotional material regarding Cancidas.

PANEL RULING

The Panel noted that Section 4.2 of the Cancidas summary of product characteristics (SPC) read 'Caspofungin acetate has not been studied in paediatric patients. Use in patients under 18 years of age is not recommended'. Merck Sharp & Dohme had instructed its mailing house to distribute the letter to, *inter alia*, hospital specialists involved in the treatment of patients with fungal disease. That list included haematologists but not paediatricians. The Panel noted that the letter had been received by a consultant paediatric haematologist. The Panel did not consider that the instructions given to the mailing house were unreasonable given the product's licensed indication and did not consider that the distribution of the letter as described amounted to the promotion of Cancidas outwith the terms of its marketing authorization or was otherwise inconsistent with its SPC. The first paragraph of the letter clearly stated that Cancidas had received its licence for use in adult patients. No breach of Clause 3.2 was ruled.

APPEAL BY GILEAD SCIENCES

Gilead Sciences noted that Merck Sharp & Dohme and the Panel had acknowledged that Cancidas was not licensed for administration to patients under the age of 18 years as stated in the Cancidas SPC.

The Panel had noted that the letter had been received by a consultant paediatric haematologist. The ruling stated 'The Panel did not consider that the instructions given to the mailing house were unreasonable given the product's licensed indication and did not consider that the distribution of the letter as described amounted to the promotion of Cancidas outwith the terms of its marketing authorization or was otherwise inconsistent with its SPC'.

The instructions provided by Merck Sharp & Dohme to the mailing house described the direct distribution of the Cancidas letter to all physicians specialising in oncology, AIDS, HIV, haematology, microbiology, transplant medicine and intensive care; it was,

however, not apparent that any direction was provided with regard to the extent or nature of hospitals that should be targeted. This was somewhat contrary to directions listed in the briefing document provided by the mailing house stating that the pharmaceutical company was to 'be specific and give as much detail as possible' when providing its data requirements. Gilead Sciences stated that whilst it could understand the inadvertent distribution of this letter to paediatric physicians practising within the above specialities at hospitals known to treat both adult and paediatric patients, it could not appreciate its distribution to hospitals clearly and widely known to treat only children. There were 16 specialist paediatric hospitals in the UK and, as such Merck Sharp & Dohme could have easily given its mailing house sufficiently detailed instructions to prevent the letter being sent to doctors based exclusively within paediatric hospitals. This would have ensured that Cancidas was promoted in accordance with the terms of its marketing authorization. Gilead Sciences appealed the ruling of no breach of Clause 3.2.

COMMENTS FROM MERCK SHARP & DOHME

Merck Sharp & Dohme strongly denied that it had ever sought to promote Cancidas to paediatricians. Gilead Sciences had stated that a consultant paediatric haematologist received this letter and that this was sufficient to claim unlicensed promotion of Cancidas. The Panel had noted that instructions to the mailing house for distribution of the publication alert were not considered unreasonable, as Merck Sharp & Dohme had 'instructed its mailing house to distribute the letter to, *inter alia*, hospital specialists involved in the treatment of patients with fungal disease. That list included haematologists but not paediatricians'.

Merck Sharp & Dohme noted that Gilead Sciences now claimed that it should have told its mailing house to exclude distribution to specialist paediatric hospitals.

Merck Sharp & Dohme maintained that its activities in this regard represented very common practice in the UK; the mailing company had stated that less than 5% of briefings specified that a medicine was licensed for use in adults only. It was exceptionally rare (less than 1%) that instructions were given on which hospitals should be excluded, and even then this was not usually due to the indication of the medicine. It was much more common for instructions to be based on speciality, as Merck Sharp & Dohme had done. Had this proposed policy of giving specific instructions to exclude specialist paediatric hospitals been implemented, then the letter would not have been sent to some physicians who were involved in treating adult patients, despite being registered at such a hospital. Even in this small and highly specialised therapeutic area, Merck Sharp & Dohme knew of two doctors to whom this would apply. This would not seem to be a reasonable restriction of promotional activity. In any event, in all cases it was incumbent on companies to reinforce that the medicine was for use in adults in the letter in question. This was clearly done in the first sentence of text that followed the headline text box, stating that the licence in the UK for empirical therapy was 'in febrile, neutropenic adult patients'.

Hence Merck Sharp & Dohme fully supported the Panel's ruling that there had not been a breach of Clause 3.2.

FURTHER COMMENTS FROM GILEAD SCIENCES

Gilead Sciences noted that Merck Sharp & Dohme continued to deny any breach of the Code despite acknowledging that paediatricians working in specialist children's hospitals, treating paediatric patients only, were sent copies of the letter in question. Merck Sharp & Dohme attempted to justify its actions by claiming that: the provision of inadequate or incomplete instructions to mailing houses was common practice within the industry; if it had provided specific instructions to exclude specialist paediatric hospitals, two paediatricians who also treated adult patients would have been excluded from this mailing and this was an unreasonable restriction of promotional activity and it had reinforced the fact that Cancidas was only licensed in adult patients by stating the licensed indication at the start of the letter.

Gilead Sciences did not accept these reasons as adequate substantiation for Merck Sharp & Dohme's actions. Firstly, it did not consider it rare for pharmaceutical mailing houses to request details of the licensed indications of the medicines which they assisted in promoting. The mailing houses that Gilead Sciences had used in the past had requested this information on each occasion. Furthermore, from recent discussions with several mailing houses Gilead Sciences believed that requests for prescribing information were common practice and not a rarity as submitted by Merck Sharp & Dohme. One mailing house had stated that it was normal practice for mailing houses themselves to obtain the SPC and to stringently check the indication or posology sections to ensure that documents were being distributed and targeted at the correct group of health professionals. Subsequently, even if some pharmaceutical companies and the mailing houses with whom they liaised, were failing to take adequate precautions to avoid unlicensed promotion, this did not excuse a breach of the Code by Merck Sharp & Dohme.

Secondly, Gilead Sciences considered that it was unacceptable to risk unlicensed promotion of Cancidas to the more than forty registered UK haematologists and oncologists that treated paediatric patients only, in order to ensure that two doctors who also treated adult patients received the letter. All of the mailing houses contacted had confirmed that they would have been able to target individual physicians and were happy to receive precise detailed instructions to exclude certain hospitals or specific cohorts of doctors in order to comply with product marketing authorizations.

Gilead Sciences maintained that Merck Sharp & Dohme's actions constituted unlicensed promotion to paediatricians in breach of Clause 3.2 of the Code.

APPEAL BOARD RULING

The Appeal Board considered that as Cancidas was not indicated for use in patients aged under 18 years

of age, Merck Sharp & Dohme should have instructed its mailing house to exclude from the mailing list all doctors whose professional address was a children's hospital. The letter had been sent to a consultant paediatric haematologist at a children's hospital. The Appeal Board considered that given the product's licensed indication, the distribution of the letter as described amounted to the promotion of Cancidas outside the terms of its marketing authorization and was inconsistent with its SPC. A breach of Clause 3.2 was ruled. The appeal on this point was successful.

2 Claim 'The results from this head to head trial support the use of Cancidas as first line empirical antifungal therapy instead of AmBisome 3mg/kg/day'

COMPLAINT

Gilead Sciences stated that this claim implied that Cancidas was shown to be more efficacious in Walsh *et al* and therefore should be used instead of AmBisome. Although the bullet point following the claim stated that 'Cancidas was at least as effective as AmBisome…' the reader was left with a distinct impression that Cancidas was better than AmBisome. The study results showed that Cancidas was non-inferior to AmBisome and therefore a more balanced claim should position Cancidas as an alternative to rather than a replacement for AmBisome.

Gilead Sciences alleged that the claim misled by implication in breach of Clause 7.2 of the Code.

RESPONSE

Merck Sharp & Dohme denied a breach of the Code. It maintained that a clinician choosing between Cancidas and AmBisome as empirical therapy would not base a decision on efficacy data alone. Support for a rationale to prescribe Cancidas in this setting was provided by other elements presented in this study, which were referred to in the letter. The first of two bullet points that immediately followed the claim in question clearly refuted any assertion that superior efficacy was being claimed, as it stated 'Cancidas is at least as effective as AmBisome ...'. In choosing between these therapies however, a clinician might well also take into account the tolerability profile, which was discussed in the subsequent bullet point, and costs, which were compared later in the letter. If a clinician accepted the support that these results provided, and prescribed Cancidas, it would clearly then be 'instead of AmBisome'.

PANEL RULING

The Panel noted that the claim at issue 'The results from this head to head trial support the use of Cancidas as first line empirical antifungal therapy instead of AmBisome 3mg/kg/day' was immediately followed by two bullet points which set out the key results; 'Cancidas is at least as effective as AmBisome for empirical antifungal therapy of persistently febrile neutropenic patients, with a beneficial impact on survival' and 'Cancidas was significantly better tolerated than AmBisome with a significantly reduced nephrotoxicity profile'. The colour and the font in which the bullet points were presented caught the eye.

The Panel noted that Walsh *et al* examined the efficacy and safety of Cancidas compared with AmBisome for empirical antifungal therapy in patients with persistent fever and neutropenia. The primary analysis was designed to show whether the outcome in the Cancidas group was non-inferior to that in the AmBisome group. The primary efficacy endpoint was a favourable overall response as determined by a five-component endpoint. Secondary efficacy assessments consisted of assessments of each component of the primary endpoint. In relation to overall response the study authors noted that Cancidas fulfilled the statistical criteria for non-inferiority to AmBisome and concluded that Cancidas was as efficacious as AmBisome in patients with persistent fever and neutropenia and was, overall, better tolerated than AmBisome. It offered a new option for empirical antifungal therapy.

The Panel did not accept that the claim at issue implied greater efficacy for Cancidas compared with AmBisome as alleged. The claim referred to 'results' and so was likely to relate to more than one parameter. The Panel considered that the claim implied that Cancidas was an alternative first line antifungal therapy to AmBisome and noted that the following two prominent bullet points set out the reasons why that was so, ie the two were at least as effective as each other but Cancidas was significantly better tolerated. The Panel did not consider that the claim, in the context in which it appeared, was misleading as alleged. No breach of Clause 7.2 was ruled.

3 The presentation of the five individual components of the composite primary endpoint of the study

COMPLAINT

Gilead Sciences stated that over the last few years the accepted method for determining the efficacy of an antifungal agent in empiric therapy in clinical trials was the use of a composite primary endpoint the components of which were: successful treatment of baseline fungal infection; no breakthrough fungal infections during administration of study medicine or within 7 days of completion of treatment; survival for 7 days after completion of study therapy; no premature discontinuation of study medicine because of toxicity or lack of efficacy and resolution of fever during neutropenia.

Walsh *et al* deemed a patient to have been successfully treated if they fulfilled all five components of the composite endpoint. The study was powered to show non-inferiority between Cancidas and AmBisome based on the composite endpoint.

There was some debate recently regarding the statistical significance of the differences between antifungal agents when assessment was made on the basis of each of the individual components. It was generally agreed that a stricter measure of statistical significance needed to be applied to individual

components of the composite endpoints. This was confirmed in the letters by Powers *et al* (2002) and Powers (2004). Powers was an independent reviewer for the Food and Drug Administration (FDA). In order to account for multiple comparisons in the analysis of subgroups, a statistical factor, the Bonferroni correction, needed to be applied. The p value for significance for each component endpoint was therefore around the order of $p \leq 0.01$ (rather than $p \leq 0.05$).

Gilead Sciences alleged that the presentation of the five components of the composite endpoints was misleading. Firstly, the five individual components as 'primary endpoints' in the statement 'Achievement of an overall favourable response required the patient to successfully meet all five primary end-point criteria'. Secondly, the p values for two of the components, namely, no breakthrough fungal infection and resolution of fever were described as 'ns', which Gilead Sciences took to imply 'no significance'. With the p values for the other three components being stated, and being ≤ 0.05, one could only conclude that this implied a significant difference in favour of Cancidas in each of these components of the composite endpoint. In intercompany correspondence, Merck Sharp & Dohme had acknowledged that it did not consider that any statistical correction needed to be taken into account when drawing conclusions regarding the components of the composite endpoint. This went against accepted statistical practice and the conclusions of the FDA.

Gilead Sciences alleged that Merck Sharp & Dohme's representation of the components of the composite endpoint was misleading in breach of Clause 7.2 of the Code.

RESPONSE

Merck Sharp & Dohme noted Gilead Sciences' allegation that it had attempted to express the five individual components as primary endpoints by using the statement 'Achievement of an overall favourable response required the patient to successfully meet all five primary end-point criteria'. Merck Sharp & Dohme suggested that this was a matter of interpretation, but was not misleading or in breach of the Code. Although Merck Sharp & Dohme strongly maintained that this statement did not imply that there was any more than a single primary endpoint it had offered to alter all future promotional material to further clarify this matter, referring instead to 'five components of the primary endpoint'. Gilead Sciences had not acknowledged this in its complaint.

Secondly Gilead Sciences had noted that while two components of the endpoint were annotated as 'ns' (which it correctly interpreted as 'non-significant'), numerical p values were provided for the other three components. As these were ≤ 0.05, Gilead Sciences stated that a statistically significant difference in favour of Cancidas was implied for each of these components. Gilead Sciences suggested that the Bonferroni correction should be applied to individual components of the composite endpoint. It was around this issue in particular that Gilead Sciences stated that 'There has been some debate recently'.

Merck Sharp & Dohme agreed that there was some discussion within this area, but it contended that it was just debate and it considered it would not be appropriate for it to be found in breach of the Code for distributing material the content of which was supported by one of the opposing viewpoints of a debate which had not been concluded.

To substantiate its complaint, Gilead Sciences had provided two published letters from Powers (2002 and 2004). Powers was an independent reviewer from the FDA but there was no indication that his views represented those of the FDA, contrary to the claim made by Gilead Sciences.

Powers *et al* (2002) referred to studies in which the primary endpoint was not met which was clearly not the case with Walsh *et al*. Powers (2004) was published some time after the 'Dear Healthcare Professional' letter was distributed, and also after the intercompany discussions. Powers *et al* (2004) contained the statement that appeared to represent the cornerstone of Gilead Sciences' case, viz. 'When evaluating subgroup analyses [4] of the components of the composite end point, one should not consider a p value of .05 to be significant'. However, Powers misused his own reference [4] in this statement. The paper referred to was prompted by a study in which the primary endpoint was not met, and largely concerned itself with this scenario. This distinction was not made clear in Powers' letter but effectively removed it from the discussion of the case under review. Furthermore, when considering the use of the Bonferroni adjustment to account for multiple testing, the author stated 'This is too high a price to pay, however, since we are not equally interested in all the statistical tests, and the statistical adjustment increases the probability of failing to detect a true effect of treatment'.

Thus, neither of the two letters quoted by Gilead Sciences actually supported the complaint.

Merck Sharp & Dohme noted that a paper published in the BMJ entitled 'What's wrong with Bonferroni adjustments' provided a detailed assessment of the use of Bonferroni adjustments in biomedical research (Perneger 1998). It noted that the technique was developed to apply the logic of statistical tests to repetitive situations, and that it was well suited to that purpose. However, in biomedical research, the author noted that 'some statisticians and journal editors demand that a more stringent criterion be used for 'statistical significance' than the conventional $P<0.05$. Many well meaning researchers, eager for methodological rigour, comply without fully grasping what is at stake'. The paper 'advances the view, widely held by epidemiologists, that Bonferroni adjustments are, at best, unnecessary and, at worst, deleterious to sound statistical inference'. The author's concluding comment was that Bonferroni adjustments 'should not be used when assessing evidence about specific hypotheses'. The secondary endpoints described in the mailing in question were indeed predefined, specific analyses, and thus these views were directly relevant to this discussion.

In conclusion, therefore, Merck Sharp & Dohme denied that this aspect of the letter at issue was in breach of the Code.

PANEL RULING

The Panel considered that the claim at issue 'Achievement of an overall favourable response required the patients to successfully meet all five primary end-point criteria' was ambiguous. Those familiar with Walsh *et al* would understand it, however those who were not might assume that there were five primary endpoints. Nowhere in the letter was it clearly stated that the primary endpoint was a composite of five criteria. The Panel considered that the claim was misleading as alleged. A breach of Clause 7.2 was ruled. This ruling was not appealed.

The Panel noted the parties' submissions with regard to the Bonferroni correction. It appeared that there was no consensus on when or if it should be applied. The Panel noted that in Walsh *et al* it was prespecified that secondary efficacy assessments would consist of assessments of each component of the primary endpoint. These were the results which were reported in the letter; results with a p value of >0.05 had been reported as non-significant. The Panel considered that given that the secondary efficacy assessments were prespecified and that the letter clearly stated the statistical significance of each one, the representation of the components of the composite endpoint was not misleading as alleged. No breach of Clause 7.2 was ruled. This ruling was appealed.

APPEAL BY GILEAD SCIENCES

Gilead Sciences noted that with regard to the presentation of the data relating to the results of the five components of the composite endpoint, Merck Sharp & Dohme described the p values for two of them ie 'no breakthrough fungal infection' and 'resolution of fever' as 'ns', which it had acknowledged meant 'no significance'. The p values for the other three components were however provided with all three being ≤ 0.05. This representation of the data made it likely that the reader would assume that the three components of the composite endpoint accompanied by a p value represented a statistically significant difference in favour of Cancidas and it was not apparent if a multiplicity adjustment had been applied.

Moreover, as acknowledged by both Merck Sharp & Dohme and the Panel, there was currently a lack of consensus regarding the use of the Bonferroni correction as a means to reduce errors in studies with multiple secondary endpoints. In the letter no statistical correction was applied to adjust for multiple comparisons when the p values were presented for each of the five components of the composite endpoint and this was not made evident to the reader. Thus importantly, the reader would be unaware that the quoted p values of less than 0.05 might not necessarily demonstrate significance. In this context therefore Gilead Sciences considered Merck Sharp & Dohme's presentation of the five individual components of the composite endpoint to be misleading in that it implied that p values > 0.05 were not significant and that those < 0.05 were significant. Gilead Sciences alleged that by presenting all numerical p values, inaccuracies and inconsistencies in the interpretation of data would be limited.

Of additional importance was that due to the way in which the data was currently presented, a health professional would be unable to apply a multiplicity adjustment in their own interpretation of the results without consulting Walsh *et al* as not all of the numerical p values were displayed within the letter. The information was therefore presented in an unbalanced manner and was potentially misleading.

Gilead Sciences noted the requirements of Clause 7.2 and further, its supplementary information which referred to emerging clinical or scientific opinion and 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 in promotional material. Hence Gilead Sciences alleged that the representation of the results did not reflect the on-going debate regarding the use of the Bonferroni correction, did not enable the physician to apply the statistical correction if they wished, and thus clearly provided a biased representation from the study.

Gilead Sciences stated that the fairer representation would be the inclusion of numerical p values for all components of the composite endpoint. Further clarity should be provided in the form of a statement such as 'no adjustment has been made for multiple comparisons' to make clinicians aware that adjustment for multiple comparisons had been applied and to allow them to draw their own conclusions on the data.

Gilead Sciences alleged that the letter did not reflect a balanced, objective and unambiguous representation of the data in breach of Clause 7.2 of the Code.

COMMENTS FROM MERCK SHARP & DOHME

Merck Sharp & Dohme noted that the essence of Gilead Sciences' complaint in this point referred to a proposed need for multiplicity adjustment in the presentation of p values for the components of the primary endpoint that were listed in the letter. It was important to note that these components were themselves pre-defined as secondary endpoints in the study. As Gilead Sciences stated, p values were given for three of these components, (ranging from 0.03 to 0.05), while for the other two it was stated that p=ns, signifying no statistical significance.

In previous correspondence, Gilead Sciences had claimed that an adjustment such as the Bonferroni correction should have been used here for the analysis of multiple secondary endpoints. Merck Sharp & Dohme had provided evidence that such a correction was not recommended for use in scenarios such as this. The Panel had accepted that there was no consensus on this, but 'considered that given the secondary efficacy assessments were prespecified and that the letter clearly stated the statistical significance of each one, the representation of the components of the composite endpoint was not misleading as alleged'.

Merck Sharp & Dohme noted that in adding to its complaint, Gilead Sciences had mainly focussed on proposing that the reader should have been made

aware that no statistical correction was applied to adjust for multiple comparisons when the p values were presented. Gilead Sciences had quoted from Clause 7.2, stating that care should be taken to ensure that an issue should be treated in a balanced manner if it had not been resolved in favour of one generally accepted viewpoint.

Merck Sharp & Dohme maintained that following the references provided by it previously, the most widely accepted viewpoint in this matter was that such a statistical correction was not required. Merck Sharp & Dohme trusted that the Appeal Board would agree that standard practice in the industry would be to quote secondary endpoints in this fashion, with no requirement to use correction or to state that such adjustment had not been used. Furthermore, no requirement for a correction factor was stated in the design of the study.

Merck Sharp & Dohme re-emphasised that Gilead Sciences was only able to quote from one individual to support its case in this matter. Powers misused one of his own references which related to a study in which the primary endpoint was not met, and which was therefore not relevant in this discussion on Walsh *et al*, in which the primary endpoint was met.

Merck Sharp & Dohme did not understand why Gilead Sciences claimed that p values for all five secondary endpoints should be given to allow the reader to apply their own multiplicity adjustment. The only two endpoints for which p values were not given clearly had p values already greater than 0.05, and it was difficult to see why anyone would wish to apply a correction factor to these p values, as they were already statistically not significant.

Merck Sharp & Dohme strongly considered that its interpretation of the results from Walsh *et al* did not render its portrayal of them misleading. Merck Sharp & Dohme therefore supported the Panel's ruling that there was no breach of Clause 7.2.

FURTHER COMMENTS FROM GILEAD SCIENCES

Gilead Sciences noted that Merck Sharp & Dohme acknowledged that there was ongoing debate within the medical and scientific community regarding the application of a statistical correction to multiple secondary endpoints in clinical trials; a debate 'which has not been concluded'. The Panel also acknowledged this lack of consensus. However, in its response to the appeal, Merck Sharp & Dohme stated that the most widely accepted viewpoint in this matter was that such a statistical correction was not required.

Gilead Sciences alleged that there was currently no evidence available to support the claim that one view point was more widely accepted than the other, and it knew of several publications supporting the use of statistical corrections in accessing multiple secondary endpoints. By stating that two of the five components of the composite primary endpoint were not significant, Merck Sharp & Dohme presupposed that all readers accepted its standpoint that no multiplicity adjustment need be applied. This, therefore, misled readers that did not subscribe to this point of view.

Gilead Sciences suggested that this could be avoided in future promotional material by displaying all p values for the components of the composite primary endpoint and including a statement telling the reader that no statistical correction had been applied.

APPEAL BOARD RULING

The Appeal Board noted that in the description of the statistical analysis given by Walsh *et al*, the authors did not state, with regard to the efficacy results, what p value represented statistical significance. (This information was given for the safety analysis). In a table of results the authors stated the p values for each of the five components of the primary endpoint but did not ascribe statistical significance to any of them. In a discussion of the components of the primary endpoints the authors stated that the 'data *suggest* (emphasis added) that caspofungin-treated patients had better outcomes than patients treated with liposomal amphotericin B with respect to three of the components'. These three components were the three which, in the letter at issue, were given p values of 0.05, 0.04 and 0.03 thus, in the absence of any statement to the contrary, allowing some readers to assume that statistical significance had been proven. This was compounded by the use in the letter of p=ns for the two other components. By contrast the Appeal Board noted the authors' more cautious interpretation of the results. The Appeal Board considered that the presentation of the study results was thus misleading and ruled a breach of Clause 7.2 of the Code. The appeal on this point was successful.

4 Claim 'In addition, Cancidas demonstrated a superior tolerability profile …'

COMPLAINT

Gilead Sciences alleged that this sweeping claim was unsubstantiable in breach of Clause 7.4 of the Code. The letter offered no qualification of what constituted a 'superior tolerability profile'.

RESPONSE

Merck Sharp & Dohme could not understand how this claim could be brought into question, in the face of the strong support for it provided by the data presented in the letter and Walsh *et al*. The remainder of the sentence that Gilead Sciences highlighted referred specifically to the significant difference between Cancidas and AmBisome in the incidence of nephrotoxicity (2.6% v 11.5% respectively, $p<0.001$), an important aspect of tolerability. Furthermore, Walsh *et al* reported a number of other adverse events for which there was a significant difference in favour of Cancidas, namely infusion-related events, discontinuation of study therapy because of a medicine-related adverse event, any medicine-related adverse event, clinical medicine-related adverse events and laboratory medicine-related adverse events. Indeed, with regard to the latter two groupings of adverse events, in the 20 types of event listed, only one occurred less frequently with AmBisome, compared with 19 that were less frequent with Cancidas. In addition, for 10 of these 19 events, the positioning of the 95% confidence intervals

(by not including zero) provided further support for a more favourable outcome with Cancidas.

Merck Sharp & Dohme therefore denied a breach of Clause 7.4.

PANEL RULING

The Panel noted that, in full, the claim at issue read 'In addition, Cancidas demonstrated a superior tolerability profile with nephrotoxicity observed in 2.6% patients vs 11.5% with AmBisome ($p<0.001$)'.

Walsh *et al* concluded that fewer patients who received caspofungin sustained a nephrotoxic effect ($p<0.001$), an infusion-related event ($p<0.001$), any medicine-related adverse event ($p<0.001$) or discontinued therapy because of a medicine-related adverse event ($p=0.04$). Although the rates of medicine-related adverse events reported most frequently were similar in the two groups, several – chills, nausea, vomiting, decrease in serum potassium, elevation in serum creatinine and alkaline phosphatase level – occurred less often with caspofungin than with amphotericin B. The study authors concluded that caspofungin was overall, better tolerated than amphotericin B. The Panel thus considered that the claim at issue could be substantiated. No breach of Clause 7.4 was ruled.

5 Claim: 'This new published data, comparing Cancidas to AmBisome, provides the definitive evidence enabling Cancidas to set a new and improved standard in antifungal empirical therapy in adult neutropenic patients'

COMPLAINT

Gilead Sciences stated that this implied an efficacy advantage for Cancidas over AmBisome, which was not substantiated by Walsh *et al*. As previously discussed, the study showed *non-inferiority* of Cancidas to AmBisome. Gilead Sciences thus alleged that the claim was exaggerated, inaccurate, unbalanced and incapable of substantiation in breach of Clauses 7.2 and 7.4 of the Code.

RESPONSE

Merck Sharp & Dohme referred to its response at point 2 above. There was no mention of a claim of superior efficacy in this statement. Again, the justification for describing Cancidas as setting an 'improved standard' came not from an isolated consideration of efficacy. This was clearly expressed in the boxed text that immediately followed the claim at issue, which described Cancidas as 'At least as effective as AmBisome, with better tolerability than AmBisome, and less than half the daily cost of AmBisome'. The statements regarding efficacy and tolerability were very similar to those in the closing paragraph of the discussion in Walsh *et al*, and the claim regarding cost was valid when comparing to AmBisome 3mg/kg/day (at the time of the letter's distribution). Merck Sharp & Dohme was confident that the evidence presented supported the claim in question, and was of interest to those involved in prescribing these medicines.

PANEL RULING

The Panel considered that its comments at point 2 were relevant here. The claim would be considered in light of the letter as a whole. The Panel did not consider that the claim at issue implied an efficacy advantage for Cancidas over AmBisome. The claim summarized the data which had already been presented ie that Cancidas was at least as effective as AmBisome but better tolerated. No breach of Clauses 7.2 and 7.4 was ruled.

APPEAL BY GILEAD SCIENCES

Gilead Sciences noted that the Panel had ruled no breach of the Code because it considered that the claim had 'summarised the data which had already been presented' within the balance of the letter, this being that 'Cancidas was at least as effective as AmBisome but better tolerated'. However, Gilead Sciences alleged that this claim was misleading and inaccurate, in breach of Clauses 7.2 and 7.4, for a number of reasons. Use of the word 'definitive' implied that the data obtained from Walsh *et al* was final and decisive.

Supporting data comparing the efficacy and safety of Cancidas to AmBisome as empirical therapy in adult neutropenic patients was limited to the cited single non-inferiority study in which no proven efficacy advantage over AmBisome was found. More importantly, the study demonstrated that Cancidas was non-inferior to AmBisome. This was different from the proposed suggestion of a 'new and improved standard'. Therefore Gilead Sciences alleged that this study did not provide definite evidence, especially in terms of efficacy, to support Cancidas as a 'new and improved standard', and that use of the term 'definitive' in this context was misleading.

Furthermore, Gilead Sciences noted that the claim described the use of findings from Walsh *et al* as supportive evidence for Cancidas as a 'new and improved standard in antifungal empirical therapy'. By using the word 'therapy' in this context most readers were likely to perceive this statement as an efficacy claim. Additionally no definition or clarification was provided as to the nature or extent of the supporting data. Indeed Walsh *et al* described 'caspofungin to be as effective as AmBisome' but no efficacy advantage for Cancidas was demonstrated. In the absence of clarification, the implication that Cancidas provided an 'improved standard' of efficacy was clearly misleading. The claim of an improved standard could not be based upon tolerability and cost alone. In Gilead Sciences' view this data was insufficient to claim 'a new and improved standard'.

In addition, Gilead Sciences did not consider that the claim was adequately clarified by the text described in the box provided immediately below 'New Evidence: At least as effective as AmBisome, with better tolerability than AmBisome, and less than half the daily cost of AmBisome' or that present in the body of the letter. In fact the information described within the box contradicted that of the claim with regard to efficacy. The results of the non-inferiority study, Walsh *et al*, demonstrated Cancidas to be as effective

as AmBisome, as correctly stated in the 'new evidence' section however this conclusion had been misleadingly adapted within the claim. Moreover, the inclusion of the claim as a final summary to the letter with further explanation appearing below in a separate box might be interpreted as findings from two separate studies.

Finally Gilead Sciences stated that some recipients of the letter might read the claim as a general overview of the letter due to time constraints and if taken alone the summary statement was misleading. Consequently, if cited in any future correspondence without further substantiation and qualification this would provide an inaccurate reflection of Walsh *et al*.

COMMENTS FROM MERCK SHARP & DOHME

Merck Sharp & Dohme noted that Gilead Sciences now claimed that use of the word 'therapy' implied to most readers that an efficacy claim was being made. This under-laid the main premise of its latest argument on this point, and was one with which Merck Sharp & Dohme completely disagreed. Merck Sharp & Dohme maintained once again that physicians prescribing a therapy would consider more than efficacy and would include tolerability and potentially, cost.

Merck Sharp & Dohme submitted that nowhere in the letter was there any claim of superior efficacy. The prominent text box near the end of the letter clearly stated that Cancidas was 'at least as effective as AmBisome, with better tolerability than AmBisome, and less than half the daily cost of AmBisome'. Merck Sharp & Dohme maintained this was more than sufficient to make the claim in question.

Merck Sharp & Dohme strongly disagreed with Gilead Sciences that the text box contradicted an efficacy claim in the summary statement – simply because there was no efficacy claim in this statement, though Gilead Sciences had chosen to interpret it that way.

Merck Sharp & Dohme equally disagreed with Gilead Sciences' new suggestion that the use of a summary statement followed by a separate box might be interpreted as findings from two studies. The letter was labelled very prominently at the outset as a publication alert, clearly designed to inform health professionals of the results of one particular study. In the few instances that Merck Sharp & Dohme referred in the letter to other sources, they were clearly referenced as such.

Merck Sharp & Dohme found the final points raised by Gilead Sciences, regarding reading of the final paragraph alone to save time, and potential future use of the claim without substantiation, to be irrelevant. The letter should be considered in its entirety, and in its present format, and it did not consider it relevant to speculate on varying reading patterns or on hypothetical future use of a particular sentence.

Merck Sharp & Dohme found nothing in Gilead Sciences' appeal that had led it to question its defence in this matter, or to challenge the validity of the Panel's ruling.

FURTHER COMMENTS FROM GILEAD SCIENCES

Gilead Sciences alleged that the claim was inaccurate, unbalanced and incapable of substantiation in that it implied that Cancidas had an efficacy advantage over AmBisome in empiric therapy. This was not supported by the results of Walsh *et al*.

Gilead Sciences stated that in choosing between antifungal agents, a clinician would base a significant part of the decision on the comparative efficacy of the agents. Therefore, the statement that Cancidas sets a 'new and improved standard' over AmBisome could easily be taken out of context by the reader.

APPEAL BOARD RULING

The Appeal Board noted that Walsh *et al* concluded that 'caspofungin was as efficacious as liposomal amphotericin B in patients with persistent fever and neutropenia and was, overall, better tolerated than liposomal amphotericin B. Thus caspofungin provides a new option for empirical antifungal therapy in these patients'. The claim at issue, however, read 'This new published data, comparing Cancidas to AmBisome, provides the definitive evidence enabling Cancidas to set a new and improved standard in antifungal empirical therapy in adult neutropenic patients'.

The Appeal Board noted Merck Sharp & Dohme's submission that the claim encompassed considerations of efficacy, tolerability and potentially, cost. With regard to efficacy the Appeal Board noted its comments at point 3 above. With regard to tolerability the Appeal Board noted that Walsh *et al* reported less nephrotoxicity in Cancidas-treated patients compared with those treated with AmBisome, and Gilead Sciences' submission that there was no data to show whether the concomitant use of nephrotoxic medicines was equal in both groups. Overall the Appeal Board considered that the claim at issue exaggerated the findings of Walsh *et al* and particularly noted in that regard the use of the phrase 'the *definitive* (emphasis added) evidence'. A breach of Clause 7.2 was ruled. The Appeal Board further considered that the claim could not be substantiated and ruled a breach of Clause 7.4. The appeal on this point was successful.

6 Cost comparison of Cancidas to AmBisome

COMPLAINT

Gilead Sciences noted that the letter compared the average daily cost for treating a 70kg patient for 14 days with Cancidas to AmBisome at 3mg/kg/day and AmBisome 5mg/kg/day. Gilead Sciences alleged that this comparison was unfair and misleading as it compared the licensed dose of Cancidas to a higher than licensed dose of AmBisome (5mg/kg/day) in empiric therapy. In intercompany correspondence Merck Sharp & Dohme acknowledged that this was a breach of Clause 7.2 of the Code and had promised to withdraw this cost comparison from current promotional material. It had also agreed that to make such comparisons in the future.

RESPONSE

Merck Sharp & Dohme agreed that comparing costs with an unlicensed dose of AmBisome represented an inadvertent breach of Clause 7.2. This oversight was made as it was originally deemed relevant to inform health professionals of the cost of the higher AmBisome dose administered to some patients in the study, with which the letter was aimed to be as consistent as possible. Such a comparison would not be repeated in any other promotional material.

PANEL RULING

The Panel considered the cost comparison misleading as alleged and ruled a breach of Clause 7.2.

Complaint received **20 December 2004**

Case completed **14 April 2005**

CASE AUTH/1673/1/05 *NO BREACH OF THE CODE*

INSULIN DEPENDENT DIABETES TRUST v LILLY

Humalog advertisement to the public

The Insulin Dependent Diabetes Trust complained about an advertisement which had appeared in Balance, a magazine produced by Diabetes UK and intended for diabetics and their families. The advertisement which was for an insulin pump marketed by Roche Dignostics, referred to Humalog, an insulin marketed by Lilly.

The complainant alleged that a prescription only medicine, insulin, was being advertised directly to patients. In addition the advertisement was misleading because it implied that the only insulin that could be used in the pump was Humalog and as far as the complainant was aware, this was not so.

The Authority took the matter up with both Roche Diagnostics and Lilly. The Director decided that there was no *prima facie* case for Roche Diagnostics to answer as it was not a pharmaceutical company subject to the Code. In its response to the complaint Roche Diagnostics submitted that, at a European level, Lilly was aware of the advertisement at issue and had allowed its trademarks (Eli Lilly and Humalog) and the visual of the pre-filled cartridge to be used, however, Lilly did not pre-approve the advertisement at issue for use in a non-professional publication.

The Panel noted that although the advertisement was placed in a UK journal without the knowledge or authority of Lilly in the UK it was an established principle under the Code that companies in the UK were responsible under the Code for the activities of their overseas parent company or divisions. Lilly in Europe had allowed Roche Diagnostics to use its Humalog brand name in an advertisement in a UK publication. Lilly in the UK was therefore responsible under the Code for the advertisement.

The Panel considered that the advertisement was not an advertisement for Humalog insulin *per se* and so no breach of the Code was ruled in that regard. The Panel considered, however, that the advertisement would encourage patients to ask for Humalog insulin and that it was misleading as it implied that only Humalog insulin could be used in the pump which was not so. A breach of the Code was ruled.

Upon appeal by Lilly, the Appeal Board noted from the Lilly representatives that there had been no general agreement with Roche Diagnostics for the use of the Lilly trademark; Lilly USA had had a specific agreement with Roche Diagnostics Switzerland to allow it limited use of the Lilly and Humalog trademarks in specific brochures.

The Appeal Board did not consider that Lilly had consented to Roche Diagnostics' use of the Lilly and Humalog trademark in any country other than Switzerland. The Appeal Board considered that there was no evidence that either Lilly Europe or Lilly UK gave consent or were otherwise aware of use of Lilly's trademarks in the advertisement at issue. The Appeal Board ruled no breach of the Code.

The Insulin Dependent Diabetes Trust complained about an advertisement which had appeared in Balance, a magazine produced by Diabetes UK and intended for diabetics and their families. The advertisement featured the Accu-Chek D-TRONplus insulin pump and referred to its use with Humalog, an insulin marketed by Eli Lilly and Company Limited. The advertisement bore the Roche logo and the name Disetronic Medical System AG of Switzerland.

COMPLAINT

The complainant stated that the advertisement had been drawn to the Trust's attention by one of its members who was concerned that in addition to the insulin infusion pump it also advertised Humalog.

The complainant stated that while the advertisement for the D-TRONplus pump was within the Code as it was a medical device, the inclusion of a brand of insulin contravened the Code as it subtly advertised the insulin. Insulin was a prescription only medicine and as such could not be advertised directly to patients. The advertisement was also misleading because it implied that the only insulin that could be used in the pump was Humalog and as far as the complainant was aware, this was not so.

The complainant stated that the type of insulin a patient used was a clinical decision and was therefore a matter for discussion between doctor and patient. It was not to be dictated by any particular insulin delivery device and there were several insulin infusion pumps on the market that enabled patients to choose which type and brand of insulin to use.

The Authority took the matter up with both Roche Products Limited and Eli Lilly and Company Limited.

The Authority asked the companies to comment in relation to Clauses 20.1 and 20.2 of the Code.

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The Director noted that Roche Diagnostics operated as a wholly distinct company from Roche Products in the UK. Although the two companies were part of the same global organisation, Roche Diagnostics was not a pharmaceutical company subject to the Code. The Director thus decided that there was no *prima facie* case for the company to answer. In its response to the complaint, however, Roche Diagnostics stated that Lilly was aware of this advertisement from a European position. Lilly had allowed its trademarks (Eli Lilly and Humalog) and the visual image of the pre-filled cartridge to be used. However, Lilly did not pre-approve the advertisement at issue for use in a non-professional publication.

* * * * *

RESPONSE

Lilly stated that it was unaware of this advertisement issued by Roche, and had had no involvement in its development or subsequent use.

Lilly did not have any agreement regarding the promotion of insulin pumps and Humalog with Roche, either in the UK or worldwide.

PANEL RULING

The Panel noted that Clause 20.1 prohibited the advertising of prescription only medicines to the general public. Clause 20.2 permitted information to be supplied directly or indirectly to the general public but such information had to be factual and provided in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their doctor to prescribe a specific medicine.

The Panel noted Roche Diagnostics' submission that, at a European level, Lilly was aware of the advertisement at issue and had allowed it to use its trademarks (Eli Lilly and Humalog) and the visual of the pre-filled cartridge. Lilly did not pre-approve the advertisement at issue for use in a non-professional publication.

The Panel noted that although the advertisement was placed in a UK journal without the knowledge or authority of Lilly in the UK it was an established principle under the Code that companies in the UK were responsible under the Code for the activities of their overseas parent company or divisions. Lilly in Europe had allowed Roche Diagnostics to use its Humalog brand name in an advertisement in a UK publication. Lilly in the UK was therefore responsible under the Code for the advertisement.

The Panel considered that the advertisement in Balance was not an advertisement for Humalog insulin *per se* and so no breach of Clause 20.1 was ruled. The Panel considered, however, that the advertisement would encourage patients to ask for Humalog insulin.

The Panel noted that the advertisement referred to the insulin pump 'with its 3.0 ml Humalog pre-filled pen cartridges'. The Panel considered that the advertisement was misleading as it implied that only Humalog insulin could be used in the pump which was not so. A breach of Clause 20.2 was ruled.

APPEAL BY LILLY

Lilly submitted that it was not made aware of, and did not consent to, the advertisement at issue issued by Roche either on a UK or on a European level, and had had no involvement whatsoever in its development or subsequent use. Lilly reiterated that it had no agreement regarding the promotion of insulin pumps and/or Humalog with Roche Diagnostics, either in the UK or worldwide.

Lilly noted that it had in fact approved the use of the Humalog trademark and picture in a number of product brochures for Roche Diagnostic's insulin delivery system, copies of which were supplied. This approval was limited to and specific for such product brochures and did not include, or contemplate, any advertisements, either to health professionals or the general public.

In the light of the above, Lilly submitted that the Panel's ruling of a breach of Clause 20.2 was based on incorrect information and that Lilly neither could nor should be held responsible for an advertisement which was placed in the UK by a third party (Roche Diagnostics) without the knowledge or consent of either Lilly UK or Lilly globally.

COMMENTS FROM COMPLAINANT

The complainant made no further comment.

APPEAL BOARD RULING

The Appeal Board noted from the Lilly representatives that there had been no general agreement with Roche Diagnostics for the use of the Lilly trademark.

The Appeal Board noted from Lilly that Lilly USA had had a specific agreement with Disetronic (now Roche Diagnostics) Switzerland to allow it limited use of the Lilly and Humalog trademarks in specific brochures.

The Appeal Board did not consider that Lilly had consented to Disetronic's (now Roche Diagnostics) use of the Lilly and Humalog trademark in any country other than Switzerland. The Appeal Board considered that there was no evidence that either Lilly Europe or Lilly UK gave consent or were otherwise aware of Disetronic/Roche Diagnostics' use of Lilly's trademarks in the UK advertisement at issue. The Appeal Board ruled no breach of Clause 20.2. The appeal on this point was successful.

Complaint received **4 January 2005**

Case completed **30 March 2005**

CASE AUTH/1674/1/05 *NO BREACH OF THE CODE*

SANOFI-AVENTIS v PIERRE FABRE

Navelbine leaflet

Sanofi-Aventis alleged that a leaflet for Navelbine (vinorelbine), issued by Pierre Fabre, was in breach of the Code because it promoted the unlicensed combination of Navelbine and trastuzumab (Roche's product, Herceptin). Navelbine was licensed for the 'Treatment of advanced breast cancer stage 3 and 4 relapsing after or refractory to an anthracycline containing regimen'. There was no information in the summary of product characteristics (SPC) relating to its use in combination with trastuzumab.

Sanofi-Aventis noted that although clinicians commonly used chemotherapy agents in combination, this should not permit Navelbine (a cytotoxic chemotherapy agent) to be promoted with any combination of cancer treatments, merely because the SPC did not specify which agent it could be combined with. It was essential that chemotherapy agents in particular, which were generally associated with toxicity, were promoted strictly within the recommendations of the SPC.

The Panel noted that Navelbine was licensed, *inter alia*, for the treatment of advanced breast cancer stage 3 or 4 relapsing after or refractory to an anthracycline containing regimen. The Panel noted that this was a complex therapy area. The Panel noted Sanofi-Aventis' submission that many chemotherapy agents were commonly used in combination. The Panel did not consider that Navelbine's licensed indication prohibited its use in combination with trastuzumab for the treatment of advanced breast cancer as alleged. The licensed indication did not refer to either monotherapy or combination therapy. The Panel did not consider that the leaflet promoted Navelbine in a manner which was inconsistent with the particulars listed in its SPC as alleged. No breach of the Code was ruled which, on the narrow ambit of the complaint, was upheld on appeal by Sanofi-Aventis.

Sanofi-Aventis complained about a four page promotional leaflet (ref PF098) for Navelbine (vinorelbine) issued by Pierre Fabre Ltd. The leaflet set out a case scenario involving the use of Navelbine in combination with trastuzumab (Roche's product, Herceptin) in a patient with advanced breast cancer.

Navelbine was indicated, *inter alia*, for the treatment of advanced breast cancer stage 3 and 4 relapsing after or refractory to an anthracycline containing regimen.

Sanofi-Aventis marketed Taxotere (docetaxel).

COMPLAINT

Sanofi-Aventis noted that the leaflet promoted Navelbine in combination with trastuzumab; it outlined the rationale for this new combination, detailed its efficacy and toxicity and gave a recommended dose and schedule for the combination. Sanofi-Aventis stated, however, that this combination was unlicensed and alleged that such promotion was not in line with the marketing authorization for Navelbine in breach of Clause 3.2 of the Code.

Navelbine was licensed for the 'Treatment of advanced breast cancer stage 3 and 4 relapsing after or refractory to an anthracycline containing regimen'. There was no information in the summary of product characteristics (SPC) relating to its use in combination with trastuzumab.

Sanofi-Aventis noted that although it was common practice for clinicians to use many chemotherapy agents in combination in one form or another, this clearly should not permit Navelbine (a cytotoxic chemotherapy agent) to be safely promoted with any combination of cancer treatments, merely because the SPC did not specify which agent it could be combined with. It was essential that chemotherapy agents in particular, which were generally associated with toxicity, were promoted strictly within the recommendations of the SPC.

RESPONSE

Pierre Fabre stated that advanced breast cancer was fatal and treatment at this stage was intended to palliate symptoms and to delay disease progression and death. During the course of their disease, a patient would receive concomitant medication to achieve this goal or reduce the toxicity of treatment. A patient would receive multiple lines of chemotherapy as single agents or in combination. Concomitant use of appropriate supportive and alternative treatments, such as analgesics, anti-emetics, growth factors, steroids, hormones, bisphosphonates and vitamins would also be given to relieve symptoms or reduce treatment-related toxicity. Approximately 20% of patients had a tumour that over-expressed human epidermal growth factor receptor 2 (HER2) and should be treated with trastuzumab in addition to chemotherapy and supportive therapies.

Pierre Fabre explained that the leaflet was a case scenario designed to initiate a discussion about patients who had previously been treated with an anthracycline and a taxane such as, *inter alia*, docetaxel (Sanofi-Aventis' product Taxotere). The patient in this scenario was within a sub-group of patients with a tumour that over-expressed the specific receptor that made her suitable for treatment with trastuzumab (<20% patients).

Pierre Fabre explained that the patient profiled in the leaflet had previous treatment with both anthracycline and taxane. As patients were unlikely to receive the same medicines during subsequent treatment, there was no apparent conflict with any potential use of docetaxel and it was thus difficult to understand why Sanofi-Aventis had complained.

The marketing authorization for Navelbine relating to breast cancer was for the 'Treatment of advanced breast cancer stage 3 or 4 relapsing or refractory to an

anthracycline containing regimen'. This indication did not place any limit or restriction on other treatments with which Navelbine might or might not be used concurrently or sequentially. The regulatory submission for Navelbine included data from a wide range of combinations with other agents, supportive treatments and treatment modalities. A more recent National Institute for Clinical Excellence (NICE) evaluation of Navelbine in breast cancer included data and analysis of Navelbine alone or in combination with: doxorubicin, epirubicin, paclitaxel, mitoxantrone, docetaxel, 5-fluorouracil, cyclophosphamide, epirubicin plus cyclophosphamide, cisplatin, gemcitabine, ifosfamide, mitomycin-C, trastuzumab, cisplatin plus 5-fluorouracil, epirubicin plus 5-fluorouracil and doxorubicin plus methotrexate plus leucovorin. Pierre Fabre submitted that the role of NICE was to review data pertinent to the licensed use of Navelbine in the UK. By including these data, the regulatory authorities and NICE had demonstrated that the indication for Navelbine in breast cancer was open and unrestricted as written in the SPC.

There were published data identifying preclinical and clinical synergy between Navelbine and trastuzumab. There were no known overlapping toxicities, making their use together feasible and well tolerated in this small and difficult patient group and was included in the review by NICE. Information on Navelbine and trastuzumab was legitimately provided to health professionals who were managing anthracycline pre-treated patients with advanced breast cancer. This was not inconsistent with the SPC for Navelbine. Pierre Fabre thus denied a breach of Clause 3.2 of the Code.

PANEL RULING

The Panel noted that the leaflet discussed the efficacy, tolerability and dosage regimen of the Navelbine and trastuzumab combination.

The Panel noted that Navelbine was licensed, *inter alia*, for the treatment of advanced breast cancer stage 3 or 4 relapsing after or refractory to an anthracycline containing regimen. The Panel noted that this was a complex therapy area. The Panel noted Sanofi-Aventis' submission that it was common practice for many chemotherapy agents to be used in combination. The Panel did not consider that Navelbine's licensed indication prohibited its use in combination with trastuzumab for the treatment of advanced breast cancer as alleged. The licensed indication did not refer to either monotherapy or combination therapy. The Panel did not consider that the leaflet promoted Navelbine in a manner which was inconsistent with the particulars listed in its SPC as alleged. No breach of Clause 3.2 of the Code was ruled.

During its consideration of this case the Panel noted that trastuzumab was indicated for the treatment of patients with metastatic breast cancer, whose tumours over-expressed HER2, either as monotherapy or in combination with paclitaxel or docetaxel. The Panel noted that trastuzumab thus did not have an unqualified licence for combination therapy: its combination use was restricted to use with docetaxel and paclitaxel. The Navelbine leaflet at issue thus referred to the unlicensed use of trastuzumab. The leaflet was silent as to the licensed indications of trastuzumab and thus gave the impression that it was licensed for use in combination with Navelbine. That was not so. References to competitor products had to comply with the Code, in particular the requirements of Clause 7.2. The Panel was concerned that reference to the unlicensed use of trastuzumab was such that the leaflet failed to meet the requirements of Clause 7.2 on this point. The Panel requested that Pierre Fabre be advised of its concerns in this regard.

APPEAL BY SANOFI-AVENTIS

Sanofi-Aventis noted that the leaflet, which was still being used, only promoted Navelbine in combination with trastuzumab. However, the combination of these two agents was unlicensed, not in line with Navelbine's marketing authorization and therefore in breach of Clause 3.2 of the Code. The indication, as recommended in the Navelbine SPC, was for the 'treatment of advanced breast cancer stage 3 or 4 relapsing after, or refractory to, an anthracycline containing regimen'. It did not state any information relating to the use of combinations with trastuzumab.

Sanofi-Aventis noted Pierre Fabre's submission that patients would receive concomitant medication to achieve the goal of delaying disease progression and reducing toxicity of treatment. In addition, the company mentioned the use of concomitant measures such as analgesics, growth factors, steroids, hormones etc, to relieve symptoms or reduce toxicity. Those who over-expressed the HER2 receptor should therefore receive trastuzumab in addition to chemotherapy and supportive measures. This suggested that trastuzumab should be regarded as concomitant medication to other chemotherapy and other supportive measures. Sanofi-Aventis alleged that this was clearly not how trastuzumab should be viewed, as it was a targeted monoclonal antibody that could be regarded as a stand-alone treatment.

Sanofi-Aventis noted that the Herceptin (trastuzumab) SPC recommended that it should be used only:

- 'As **monotherapy** [emphasis added] for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane.
- In **combination with paclitaxel** [emphasis added] for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable.
- In **combination with docetaxel** [emphasis added] for the treatment of those patients who have not received chemotherapy for their metastatic disease.'

Sanofi-Aventis noted that trastuzumab was classed as an anti-neoplastic agent, and had its own specific list of undesirable effects, special warnings and recommendations. The indications listed in the SPC were based on registration trial evidence which carefully studied the safety and toxicities associated

with combining agents as above. Although clinicians commonly used many chemotherapy agents in one form of combination or another, irrespective of their licence, this clearly should not allow Navelbine (a cytotoxic chemotherapy agent), to be safely promoted with any combination of cancer treatments, merely because the SPC did not specify which agent it could be combined with.

Sanofi-Aventis also noted Pierre Fabre's comment that the licensed indication for Navelbine did not place any limit or restriction on other treatments with which it might or might not be used concurrently or sequentially, and that the relevant regulatory submission included data from a wide range of combinations with other agents. However, Pierre Fabre failed to specify whether this regulatory submission contained data on the combination of Navelbine with trastuzumab. It was unlikely that Pierre Fabre's submission contained any data on this combination, as the registration approval of Navelbine pre-dated the referenced studies in the leaflet.

Sanofi-Aventis stated that it was essential that chemotherapy agents which were clearly associated with toxicity, when given either as monotherapy or in combination, were promoted strictly within the evidence base submitted as part of the regulatory submission, since it considered this had not been the case with the promotion of Navelbine with trastuzumab, it appealed the Panel's decision.

COMMENTS FROM PIERRE FABRE

Pierre Fabre noted that the leaflet was a case scenario designed to initiate a discussion around patients who had been previously treated with an anthracycline and a taxane. The patient in this scenario was within a sub-group of patients with a tumour that over-expressed the specific receptor that made them suitable for treatment with trastuzumab. This patient had already been treated with both an anthracycline and a taxane and these medicines would not be considered again in her management.

The leaflet was used with health professionals involved in the management of patients with advanced breast cancer from February 2003 and was now under scheduled review after two years.

Pierre Fabre stated that advanced breast cancer was fatal and treatment at this stage was intended to palliate symptoms and to delay disease progression and death. A patient would receive multiple lines of cytotoxic chemotherapy as single agents or in combination and a number of other non-chemotherapy treatments including trastuzumab if clinically indicated (approximately 20% of patients had a tumour that over-expressed HER2 and NICE recommended these patients should be treated with trastuzumab in addition to chemotherapy and supportive therapies).

The marketing authorization for Navelbine relating to breast cancer was 'Treatment of advanced breast cancer stage 3 or 4 relapsing or refractory to an anthracycline containing regimen'. This authorization was granted in 1997, based on data on use as a single agent and in a wide range of combinations with other treatments for advanced breast cancer. Navelbine was well tolerated and active in a range of combinations and the licensing authority had not restricted its use. Additionally, there was no requirement for the clinical data reviewed in the application to be summarised in the SPC.

Pierre Fabre submitted that the unrestricted licence for Navelbine was similar to a wide range of other treatments and support therapies in oncology eg cisplatin, 5-fluorouracil, doxorubicin, epirubicin, colony stimulating factors, anti-emetics and analgesics and was consistent with the practice of oncology, where agents were combined for maximum possible patient benefit. In fact, the safe use of some particularly toxic chemotherapy agents, such as docetaxel, was only possible with the concomitant use of other treatments such as anti-emetics and high dose steroids.

NICE had reviewed Navelbine in breast cancer. The NICE 'Guide to the technology appraisal process' section 3.2.5 stated 'Unless the Department of Health or the Welsh Assembly Government indicates otherwise, appraisals do not normally include consideration of the use of a technology for indications for which regulatory approval has not been granted in the UK'.

Pierre Fabre submitted that the NICE appraisal of Navelbine in breast cancer had only considered use of this technology within its approved use. The NICE appraisal considered data and analysis on response and survival outcomes and toxicity of Navelbine in combination with: doxorubicin, epirubicin, paclitaxel, mitoxantrone, docetaxel, 5-fluorouracil, cyclophosphamide, epirubicin plus cyclophosphamide, cisplatin, gemcitabine, ifosfamide, mitomycin-C, trastuzumab, cisplatin plus 5-fluorouracil, epirubicin plus 5-fluorouracil and doxorubicin plus methotrexate plus leucovorin. Pierre Fabre submitted that by granting this licence and including all these data, the regulatory authorities and NICE had clearly demonstrated that the indication for Navelbine in breast cancer was open and unrestricted as in the SPC.

Pierre Fabre submitted that the leaflet in question provided information on the concomitant use of Navelbine and trastuzumab which was not inconsistent with the Navelbine SPC.

FURTHER COMMENTS FROM SANOFI-AVENTIS

Sanofi-Aventis had no further comments.

APPEAL BOARD RULING

The Appeal Board noted that the leaflet discussed the rationale, efficacy, tolerability and dosage regimen of Navelbine and trastuzumab in combination.

The Appeal Board noted that Navelbine was licensed, *inter alia*, for the treatment of advanced breast cancer stage 3 or 4 relapsing after or refractory to an anthracycline containing regimen. This was a complex therapy area and it was common practice for many chemotherapy agents to be used in

combination. The leaflet was aimed at those health professionals who would be familiar with combination therapy. The Appeal Board did not consider that Navelbine's licensed indication prohibited its use in combination with trastuzumab for the treatment of advanced breast cancer as alleged. The licensed indication did not refer to either monotherapy or combination therapy. The Appeal Board did not consider that the leaflet promoted Navelbine in a manner which was inconsistent with the particulars listed in its SPC as alleged. Thus on the narrow ambit of the complaint the Appeal Board upheld the Panel's ruling and no breach of Clause 3.2 of the Code was ruled. The appeal on this point was unsuccessful.

During its consideration of this case the Appeal Board raised concerns about the leaflet in relation to the requirements of Clause 7.2. Firstly the Appeal Board noted that trastuzumab was indicated for the treatment of patients with metastatic breast cancer, whose tumours over-expressed HER2, either as monotherapy or in combination with paclitaxel or docetaxel. The Appeal Board noted that trastuzumab thus did not have an unqualified licence for combination therapy; its combination use was restricted to use with docetaxel and paclitaxel. The leaflet in question gave the impression that it was licensed for use in combination with Navelbine and that was not so. References to competitor products had to comply with the Code, in particular the requirements of Clause 7.2.

Further the Appeal Board was concerned that the section headed 'Recommended dose and schedule' gave the impression that the dosage regimen set out therein for the Navelbine and trastuzumab combination was set out in each product's marketing authorization and that was not so. The dose and schedule stated was in fact that used by Burstein (2001) to which much of the leaflet was referenced.

The Appeal Board was concerned that the leaflet failed to meet the requirements of Clause 7.2 on these points. The Appeal Board requested that Pierre Fabre be advised of its concerns in this regard.

Complaint received **15 January 2005**

Case completed **28 April 2005**

CASE AUTH/1677/2/05

GILEAD SCIENCES/DIRECTOR v PFIZER

Promotion of Vfend

Gilead Sciences complained about a double page spread, issued by Pfizer, which was published in the International Review of Patient Care 2005, the official year book of the International Hospital Federation. The left hand page took the form of a Vfend (voriconazole) advertorial entitled 'Pharmacoeconomics of invasive *Aspergillus* infections'; it had been written by an employee of the worldwide outcomes research arm of Pfizer based in America and discussed Vfend, a broad spectrum antifungal agent, indicated, *inter alia*, for the treatment of invasive aspergillosis, in relation to its cost effectiveness and value of treatment. The right hand page was a traditional style one page advertisement for Vfend. Gilead Sciences also complained about a letter sent to UK recipients of the International Review of Patient Care which corrected an error in the advertorial part of the advertisement. Gilead Sciences supplied AmBisome (liposomal amphotericin B). The part of the complaint which involved an alleged breach of undertaking was taken up by the Director as it was the responsibility of the Authority to ensure compliance with undertakings.

Gilead Sciences alleged that the claim 'Voriconazole is a relatively new first-line treatment option for invasive aspergillosis infection' was in breach of the Code. 'New' must not be used to describe any product or presentation which had been generally available, or any therapeutic indication which had been generally promoted, for more than twelve months in the UK. Vfend had been licensed and available in the UK since March 2002. Although the word 'relatively' modified the phrase it was still nonetheless inaccurate and misleading.

The Panel noted that the International Review of Patient Care was an international English language publication produced in the UK with a small UK circulation; it thus satisfied the relevant supplementary information and was subject to the Code.

The Panel also noted that although the advertorial had been placed by Pfizer's worldwide team, it was an established principle that UK companies were responsible for material subject to the Code even if it had arisen due to the acts or omissions of their overseas affiliates. Pfizer UK was thus responsible under the Code for the advertorial in question.

The Panel noted that, according to Gilead Sciences, Vfend had been licensed and available within the UK since March 2002. The use of the word 'new' and phrase 'relatively new' to describe Vfend in the 2005 edition of the International Review of Patient Care was thus contrary to the Code and a breach was ruled.

Gilead Sciences referred to Case AUTH/1553/2/04, wherein Pfizer was found in breach of the Code for making survival claims for Vfend without defining the time period for which an improvement in survival had been found (ie 12 weeks). As a consequence Pfizer had, according to the Panel, 'implied that Vfend treated patients had more chance of surviving, and recovering, than if treated

with amphotericin B whereas the data [Herbrecht *et al*] was limited to only showing the position at 12 weeks'. Within the advertorial now at issue, similar claims suggested a survival benefit with Vfend when compared with conventional amphotericin B, without referring to the 12 week study period eg 'a 12 per cent improvement in survival in clinical trials' and 'survival translates into a substantial advantage for effectiveness in cost-effectiveness analysis'.

Gilead Sciences noted that in Case AUTH/1553/2/04 the Panel had also stated that the claim 'Significantly improved survival compared with amphotericin B' was 'strong and unequivocal', but that the detail aid and leavepieces in which it appeared were distributed to an audience which would be 'familiar with the difficulty of treating systemic fungal infections' and 'the health professionals reading the material would know that such infections were associated with a high mortality rate'. The International Review of Patient Care, however, was different in that its intended audience was very likely to be misled since many of them were not involved, directly or indirectly, in the clinical management of fungal infection. Hence in accordance with Case AUTH/1553/2/04 the statement '12 per cent improvement in survival in clinical trials' could not stand alone and was in breach of the Code. Furthermore, Gilead Sciences considered the claim at issue was misleading in that it implied that survival benefit had been demonstrated in trials other than Herbrecht *et al*. This was clearly not the case.

The Panel noted that in Case AUTH/1553/2/04 it had considered that the claim 'Significantly improved survival compared to amphotericin B' implied that Vfend-treated patients had more chance of surviving, and recovering, than if treated with amphotericin B whereas the data was limited to only showing the position at 12 weeks. The claim could not stand alone. The Panel had thus considered that the claim was not adequately supported by the study as alleged; breaches of the Code were ruled.

Turning to the present case, Case AUTH/1677/2/05, the Panel noted that there were differences between the claim now at issue '[Voriconazole] has a proven efficacy advantage compared to initial treatment with amphotericin B, demonstrating superior clinical efficacy and a 12 per cent improvement in survival in clinical trials' and that considered in Case AUTH/1553/2/04. Nonetheless, the Panel considered that the claim at issue was sufficiently similar to that considered previously such that Pfizer had not complied with the undertaking given in Case AUTH/1553/2/04. A breach of the Code was ruled, as acknowledged by Pfizer.

The Panel noted that the advertorial had been placed by Pfizer's world wide team before it had been approved by Pfizer UK. Company procedure had not been followed. Whilst the Panel noted Pfizer's submission that this was an isolated incident it considered that Pfizer had not maintained high standards and that it had brought discredit upon and reduced confidence in the pharmaceutical industry; breaches of the Code were ruled.

The Panel noted that Gilead Sciences, in addition, alleged that the claim at issue was misleading as it implied that survival benefit had been demonstrated in trials other than Herbrecht *et al*. The Panel considered that whilst the claim was referenced only to Herbrecht *et al*, the use of the plural, trials, implied that there was more than one study to substantiate the claim. The Panel considered, on the evidence before it, that the claim at issue was misleading and not capable of substantiation in this regard; a breach of the Code was ruled.

Gilead Sciences alleged that the claim 'This survival translates into a substantial advantage for effectiveness in cost-effectiveness analysis' did not identify the product to which Vfend had been compared and thus was a hanging comparison which was misleading in breach of the Code. Additionally at present, no definitive publication or analysis had been conducted to demonstrate that a 12-week survival improvement resulted in a 'substantial' advantage in cost. Gilead Sciences thus alleged that this was an exaggerated claim which could not be substantiated.

The Panel noted that the claim at issue immediately followed one which compared Vfend and amphotericin B in relation to efficacy and improvement in survival. The claim at issue then began 'This survival …', thus clearly referring to the comparison in the preceding sentence. The Panel thus did not consider that the claim was a hanging comparison as alleged. No breach of the Code was ruled on this point.

The Panel acknowledged the difficulty of treating systemic fungal infections. Such infections were associated with a high mortality rate. Pfizer submitted that the 12 percent survival benefit over 12 weeks was a substantial and significant effectiveness advantage in the context of treating invasive aspergillosis infections. The Panel considered that whilst a 12 percent survival benefit over 12 weeks would have cost implications no data had been provided to substantiate this point. Pfizer had stated that the advertorial postulated that the efficacy advantages for Vfend observed by Herbrecht *et al* were *likely* (emphasis added) to lead to a favourable cost effectiveness ratio. The claim at issue, however, implied that a formal pharmacoeconomic evaluation had been undertaken which had shown a cost effectiveness advantage for Vfend versus amphotericin B; that was not so. The claim was incapable of substantiation, misleading and exaggerated as alleged. Breaches of the Code were ruled.

Gilead Sciences alleged that the claim 'Voriconazole is likely to reduce overall cost as well' implied that Vfend could potentially reduce overall cost in comparison to another agent. Neither a comparator product nor appropriate reference was cited. Gilead Sciences alleged that this statement was not capable of substantiation. Gilead Sciences also noted its general comments about pharmacoeconomic claims.

In intercompany correspondence Pfizer had stated that the sentence directly beneath the claim at issue highlighted that this related to a comparison of

Vfend and liposomal amphotericin B or caspofungin. This was misleading since the claim must be clearly substantiated, not by implied substantiation. Gilead Sciences did not know of any comparative pharmacoeconomic studies to support this claim, and indeed MIMS was cited as a reference. MIMS listed unit price and dose and did not consider overall costs as in a clinical setting. Thus this statement was misleading and could not be substantiated.

The Panel noted that the claim at issue began, and would thus be considered in the context of, a paragraph which described how Vfend might reduce costs and which included a comparison with amphotericin B and caspofungin. The Panel did not consider that the claim 'Voriconazole is likely to reduce overall costs as well' implied that Vfend could potentially reduce overall cost in comparison to another unidentified agent as alleged. No breach of the Code was thus ruled on this narrow point.

The Panel noted Gilead's allegation that there were no pharmacoeconomic studies to support the claim. MIMS was cited as a reference to the claim 'Daily drug cost for IV treatment is lower compared with liposomal amphotocin B or caspofungin' which immediately followed the claim at issue. The paragraph also mentioned the financial savings which accrued from length of hospital stay. The Panel considered that the claim at issue, 'Voriconazole is likely to reduce overall cost as well', was speculative and not capable of substantiation; a breach of the Code was ruled.

Gilead Sciences stated that the claim 'Consideration of cost-effectiveness principles reveals that initial treatment with voriconazole may offer not only a substantial efficacy advantage, but also a favourable cost benefit' lacked definition as to the product with which a comparison was made and additionally provided no quantification for the 'substantial efficacy advantage'. Gilead Sciences alleged that the claim was not capable of substantiation. Gilead Sciences also noted its general comments about pharmacoeconomic claims in relation to the claim 'This survival translates into a substantial advantage for effectiveness in cost-effectiveness analysis'.

The Panel did not consider that 'Consideration of cost-effectiveness principles reveals that initial treatment with voriconazole may offer not only a substantial efficacy advantage, but also a favourable cost benefit' was incapable of substantiation because the comparator product was not identified as alleged; it was not a comparative claim. It summarized points in the article and wherein comparators were identified. No breach of the Code was ruled on this narrow point.

In relation to the allegation that the claim was incapable of substantiation the Panel considered that its comments and rulings in the above in relation to the claims 'This survival translates into a substantial advantage for effectiveness in cost effectiveness analysis' and 'Voriconazole is likely to reduce overall cost as well' were relevant. The Panel noted the speculative nature of the claim. The Panel considered that the claim was misleading and incapable of substantiation as alleged. Breaches of the Code were ruled.

Gilead Sciences stated that in February 2005, it received multiple copies of the letter from Pfizer which attempted to address the errors made within the advertorial considered above. The last paragraph of the letter stated 'The article goes on to postulate that this survival benefit at 12 weeks is a substantial efficacy benefit which may also translate into a favourable cost-effectiveness benefit compared to other licensed antifungal agents. This work however has yet to be undertaken'. This statement suggested that despite the fact that no definitive study had investigated the efficacy or cost-effectiveness advantage of Vfend on the basis of the 12 week survival benefit, one could postulate that this would be substantial. Gilead Sciences alleged a breach of the Code on the basis that this statement was unsubstantiated, was not a fair representation of available evidence and was misleading by implication.

The Panel noted that whilst the letter stated clearly that the work to substantiate the claim had yet to be undertaken such a caveat did not negate the overriding impression that a favourable cost effectiveness benefit would be achieved. There was however no evidence to substantiate the impression given. Speculation was not an acceptable basis for claims. To claim that something *may* happen rarely negated the impression that it would. The Panel considered the statement misleading and incapable of substantiation as alleged and breaches of the Code were ruled.

Gilead Sciences stated that Pfizer's behaviour in relation to this matter was of grave concern. Not only had it breached the Code by making misleading claims in the advertorial, it had gone against an intercompany agreement and widely distributed a clarification letter making further misleading claims. The advertorial was placed without the knowledge of Pfizer in the UK and this lack of control also caused concern. Gilead Sciences alleged that Pfizer had brought discredit to and reduced confidence in the pharmaceutical industry in breach of Clause 2 of the Code.

The Panel noted its comments and rulings above in relation to the breach of undertaking; including a ruling of a breach of Clause 2. The Panel considered that the allegations about the claims in the advertorial and comment on the company's policies and procedures were covered by its ruling above. The Panel did not consider that any points additional to the breach of undertaking warranted a further ruling of a breach of Clause 2 which was reserved as a sign of particular censure. No breach of Clause 2 was thus ruled.

Gilead Sciences Limited complained about the promotion of Vfend (voriconazole) by Pfizer Limited; intercompany discussions had failed to resolve Gilead Sciences' concerns. The material at issue comprised a double page spread published in the International Review of Patient Care 2005, the official year book of the International Hospital Federation. The left hand side of the double page spread took the form of an

advertorial and was entitled 'Pharmacoeconomics of invasive *Aspergillus* infections'. The advertorial was written by an employee of the worldwide outcomes research arm of Pfizer based in America and discussed Vfend in relation to its cost effectiveness and value of treatment. The right hand side of the double page spread was a traditional style one page advertisement for Vfend (ref VFE 562). Gilead Sciences also complained about a letter sent to UK recipients of the International Review of Patient Care which corrected an error in the advertorial part of the advertisement.

Vfend, a broad spectrum antifungal agent, was indicated, *inter alia*, for the treatment of invasive aspergillosis. Gilead Sciences supplied AmBisome (liposomal amphotericin B).

The part of the complaint which involved an alleged breach of undertaking was taken up by the Director as it was the responsibility of the Authority to ensure compliance with undertakings. This accorded with advice given by the Code of Practice Appeal Board.

GENERAL COMMENTS BY GILEAD SCIENCES

The International Review of Patient Care was distributed annually to over 10,000 health professionals globally; these included medical directors in the pharmaceutical industry, pharmacists, primary care physicians, senior consultants, hospital directors, government associations and patient groups. The circulation list included some who had actively subscribed and others to whom it was sent unsolicited. Gilead Sciences considered that despite its worldwide distribution the content was subject to the Code on the basis that it was created and distributed from the UK.

Gilead Sciences had informed Pfizer of its dissatisfaction with the advertorial and the potential breaches of the Code in November 2004. Gilead Sciences had asked Pfizer to take urgent action to prevent any further distribution of the advertorial and to write to all UK recipients retracting the article and clarifying all misleading statements made within. Gilead Sciences was, however, subsequently reassured that a clarifying letter would be issued which it would be able to review and approve prior to distribution.

Gilead Sciences considered that the letter inadequately addressed its serious concerns. Additionally, little attempt had been made to clarify all of the misleading statements with only one actually being addressed. Gilead Sciences expressed reservations about the letter but Pfizer advised that the letter had been sent to the entire distribution list in anticipation of further action being taken by Gilead Sciences. Gilead Sciences had now received multiple copies of this letter as part of the unsolicited mailing list.

Gilead Sciences stated that despite Pfizer being given ample opportunity to adequately manage and diffuse this situation, it had failed to comply with an intercompany agreement or to appropriately acknowledge all misleading claims made in the advertorial to members of the health industry. Pfizer had also failed to act in the best interests of the industry by refusing to retrieve the advertorials from the UK recipients as Gilead Sciences had requested.

Gilead Sciences understood that the advertorial in question was placed in error by Pfizer's US parent company. This implied that Pfizer UK had neither seen nor reviewed this advertorial and thus had no adequate system in place in the UK for the approval of promotional materials, produced by international colleagues, for publication in UK based periodicals and journals. This was unacceptable and was of particular concern.

GENERAL COMMENTS BY PFIZER

Pfizer noted that the distribution list of the journal was truly global, with a total circulation of 10,800 across Europe, North America, Central and South America, Australasia and Pacific Rim, Asia, South East Asia, Africa, Middle East and North Africa. Less than 15% of the circulation was in the UK (1,550/10,800). The journal was published in and had a small readership in the UK.

The distribution list included presidents, chief executive officers, heads of hospitals, heads of medical specialities, heads of pharmacy, IT, purchasing, facilities and finance directors and other executives in hospitals, clinics and health authorities worldwide as well as members of the International Hospital Federation.

Pfizer considered that as the publication was a one-off annual publication, a simple erratum in the next edition would not have been appropriate.

Pfizer noted that Gilead Sciences had stated that the letter was distributed to a wider audience than received the original journal. The journal had confirmed that the letter of correction was sent '… to the UK including Ireland only', and that '… these letters were sent only to recipients of the International Review of Patient Care and to no others'.

Pfizer stated that the advertorial appeared with a Vfend advertisement as one side of a double-page spread.

Pfizer stated that Gilead Sciences' version of events leading to the formal complaint was inaccurate.

Pfizer noted that Gilead Sciences had asked it to take urgent action to prevent any further distribution of the advertorial. The initial email from Gilead Sciences was received on Friday, 12 November 2004. Pfizer ensured, through discussion with the journal editor on the next working day that there would be no further distribution of the journal.

Following discussion between it and the journal, it was not considered feasible to effectively withdraw the advertorial from circulation. Gilead Sciences was told of this on 23 November 2004 and it acknowledged the likely ineffectiveness of an attempt to withdraw the journal from circulation. As a compromise it was agreed that Pfizer would consider sending a letter of clarification to the UK distribution list.

Pfizer was particularly concerned by the allegation that it had failed to act in the best interests of the

industry by refusing to retrieve the advertorials from the UK recipients. Pfizer did not refuse. The decision not to pursue withdrawal was made jointly by Pfizer and Gilead Sciences on the grounds of feasibility.

Pfizer noted that it responded to Gilead Sciences' in early December 2004, detailing actions taken to date, which had included liaison with the publisher, Pfizer world wide team and Pfizer field force.

Pfizer decided to send a letter of clarification. Pfizer agreed to send the letter to Gilead Sciences to allow it an opportunity to review and approve it prior to sending it to the journal's distribution list. However, instead of providing comment Gilead Sciences did not communicate formally again and referred the matter directly to the Authority. Hence, contrary to the assertions made, Pfizer had co-operated fully with Gilead Sciences. Although Gilead Sciences had refused to comment on the proposed letter of clarification despite the intercompany agreement that it would provide input and feedback of the version drafted by Pfizer, it was considered that the letter needed to be sent out as any further delay was unacceptable. Hence Pfizer rectified the situation by sending a letter of clarification to the UK distribution list as had been requested by Gilead Sciences.

A Advertorial

1 Claim 'Voriconazole is a relatively new first-line treatment option for invasive aspergillosis infection'

COMPLAINT

Gilead Sciences noted that Clause 7.11 of the Code clearly stated that the word 'new' must not be used to describe any product or presentation which had been generally available, or any therapeutic indication which had been generally promoted, for more than twelve months in the UK. As Vfend had been licensed and available within the UK since March 2002, Gilead Sciences considered that this statement did not comply with the Code and was in breach of Clause 7.11. The word 'new' also appeared within the introduction of the advertorial.

In intercompany correspondence Pfizer had stated that the word 'relatively' was used in this context to modify the statement and therefore should not be considered an absolute definition. It considered that the word 'new' in this statement did not contravene the Code. Pfizer however would refrain from using the phrase 'relatively new' in all future promotional material.

Gilead Sciences agreed that the use of the word 'relatively' did somewhat modify the phrase but in line with the Code use within this context was inaccurate and misleading in breach of Clause 7.11.

RESPONSE

Pfizer stated that since the word 'relatively' was used to modify 'new', the statement was not considered an absolute definition and therefore did not contravene Clause 7.11 of the Code. Pfizer had agreed, however, in future communications to refrain from using the phrase 'relatively new'.

Furthermore the journal had a global audience. In many of the relevant countries Vfend would be considered as a 'new' treatment option for invasive aspergillosis infection.

PANEL RULING

The Panel noted the supplementary information to Clause 1.1 of the Code, Journals with an International Distribution, which stated that the Code applied to the advertising of medicines in professional journals which were produced in the UK and/or intended for a UK audience. International journals which were produced in English in the UK were subject to the Code even if only a small proportion of their circulation was to a UK audience.

The Panel noted that the International Review of Patient Care was an international English language publication produced in the UK with a small UK circulation; it thus satisfied the relevant supplementary information and was subject to the Code.

The Panel also noted that although the advertorial had been placed by Pfizer's worldwide team (Pfizer's response to point 2 below refers) it was an established principle that UK companies were responsible for material subject to the Code even if it had arisen due to the acts or omissions of their overseas affiliates. Pfizer UK was thus responsible under the Code for the advertorial in question.

The Panel noted Pfizer's submission that the journal had a global audience and thus in many countries Vfend would be considered a new treatment. The Panel noted its decision above that the journal was subject to the requirements of the Code and the advertorial would thus be judged accordingly.

The Panel noted that, according to Gilead Sciences, Vfend had been licensed and available within the UK since March 2002. The use of the word 'new' and phrase 'relatively new' to describe Vfend in the 2005 edition of the International Review of Patient Care was thus contrary to Clause 7.11 of the Code; a breach of that clause was ruled.

2 Claim '[Voriconazole] has a proven efficacy advantage compared to initial treatment with amphotericin B, demonstrating superior clinical efficacy and a 12 per cent improvement in survival in clinical trials'

COMPLAINT

Gilead Sciences referred to Case AUTH/1553/2/04, Media/Director v Pfizer wherein Pfizer was found in breach of Clauses 7.2, 7.3 and 7.4 for making claims referenced to Herbrecht *et al* (2002) which could not be adequately supported by the study itself. That complaint had concerned the claim 'Significantly improved survival compared to amphotericin B'. Some of the concerns raised in the complaint were generated because Pfizer had not defined the time period for which an improvement in survival had been found (ie 12 weeks) and as a consequence had, according to the Panel, 'implied that Vfend treated patients had more chance of surviving, and

recovering, than if treated with amphotericin B whereas the data [Herbrecht *et al*] was limited to only showing the position at 12 weeks'.

Within the advertorial at issue, similar claims suggested a survival benefit with Vfend when compared with conventional amphotericin B, without referring to the 12 week study period (eg 'a 12 per cent improvement in survival in clinical trials' and 'survival translates into a substantial advantage for effectiveness in cost-effectiveness analysis').

Gilead Sciences noted that additionally, in Case AUTH/1553/2/04 the Panel stated that the claim 'Significantly improved survival compared with amphotericin B' was 'strong and unequivocal', but that the detail aid and leavepieces in which it appeared were distributed to an audience which would be 'familiar with the difficulty of treating systemic fungal infections'. The Panel also stated that 'the health professionals reading the material would know that such infections were associated with a high mortality rate'. However, the circumstances were not the same for the distribution of the International Review of Patient Care. As such, distribution to the intended audience of that publication was very likely to mislead since many of this audience were not involved, directly or indirectly, in the clinical management of fungal infection. Hence in accordance with Case AUTH/1553/2/04 the statement '12 per cent improvement in survival in clinical trials' could not stand alone and was thus in breach of Clauses 7.2, 7.3 and 7.4 of the Code.

Furthermore, Gilead Sciences considered the claim at issue was misleading in that it implied that survival benefit had been demonstrated in trials other than Herbrecht *et al*. This was clearly not the case.

In relation to the alleged breach of undertaking the Authority asked Pfizer to respond in relation to Clauses 2, 9.1 and 22 of the Code.

RESPONSE

Pfizer accepted that the claim at issue was in breach of Clause 22 as the journal was published in the UK and had a small UK readership. It was included in the advertorial following an individual error and represented an isolated occurrence for which Pfizer apologised.

Pfizer noted that the advertorial was sent to Pfizer UK by the world wide team for comment and approval, but that the advertorial was inadvertently placed with the journal before approval from Pfizer UK had been received and so was not appropriately amended. Pfizer had in place a system of regular communication between the world wide teams and the UK affiliate teams for all medicines promoted. Part of this communication included education and reminders of the need for UK approval of promotional material placed by the world wide team in all journals relevant to the UK. Unfortunately, on this occasion, the procedure was not followed.

Furthermore, Pfizer had reminded the team involved in this isolated instance of the need to comply with the Code and of the importance of the approval by Pfizer UK of any promotional or educational material that would appear in the UK. Processes were thus in place and further comprehensive and immediate action was taken to minimize any chance of recurrence.

In relation to the alleged breach of Clause 9.1 Pfizer restated that this was an isolated, individual error, the company maintained the highest standards throughout the episode, and therefore denied a breach of Clause 9.1. Pfizer had made every effort to collaborate with Gilead Sciences and resolve the situation satisfactorily. Pfizer referred to its version of events as above.

Pfizer did not consider that its actions constituted a breach of Clause 2. Following an individual, isolated error, every effort, as noted in its general comments above, was made to liaise with the Pfizer world wide team, the Pfizer field force and to collaborate with Gilead Sciences to resolve this situation.

PANEL RULING

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

The Panel noted that in Case AUTH/1553/2/04 it had considered, on balance, that despite the intended audience of a detail aid and leavepiece (haematologists, microbiologists and intensive care physicians) and additional information provided about the study on some pages of the materials, the claim at issue 'Significantly improved survival compared to amphotericin B' implied that Vfend-treated patients had more chance of surviving, and recovering, than if treated with amphotericin B whereas the data was limited to only showing the position at 12 weeks. The claim could not stand alone. The Panel had thus considered that the claim was not adequately supported by the study as alleged; breaches of Clauses 7.2, 7.3 and 7.4 were ruled.

Turning to the present case, Case AUTH/1677/2/05, the Panel noted that there were differences between the claim at issue '[Voriconazole] has a proven efficacy advantage compared to initial treatment with amphotericin B, demonstrating superior clinical efficacy and a 12 per cent improvement in survival in clinical trials' and that considered in Case AUTH/1553/2/04; the claim at issue referred to initial treatment; no details about Herbrecht *et al* were provided and the week 12 timepoint was not referred to. Nonetheless, the Panel considered that the claim at issue was sufficiently similar to that considered previously such that Pfizer had not complied with the undertaking given in Case AUTH/1553/2/04. A breach of Clause 22 was ruled, as acknowledged by Pfizer.

The Panel noted that the advertorial had been placed by Pfizer's world wide team before it had been approved by Pfizer UK. Company procedure had not been followed. The team involved had been reminded of the need to comply with the Code in this regard. Whilst the Panel noted Pfizer's submission

that this was an isolated incident it considered that Pfizer had not maintained high standards and that it had brought discredit upon and reduced confidence in the pharmaceutical industry; breaches of Clauses 9.1 and 2 were ruled.

The Panel noted that Gilead Sciences had alleged that the claim at issue was in breach of Clauses 7.2, 7.3 and 7.4 of the Code; the Panel considered that these allegations were in effect covered by its ruling of a breach of undertaking above and thus made no further ruling on this point.

The Panel noted that Gilead Sciences, in addition, alleged that the claim at issue was misleading as it implied that survival benefit had been demonstrated in trials other than Herbrecht *et al*. Pfizer had not responded on this point. The Panel considered that whilst the claim was referenced only to Herbrecht *et al*, the use of the plural, trials, implied that there was more than one study to substantiate the claim. The Panel considered, on the evidence before it, that the claim at issue was misleading and not capable of substantiation in this regard; breaches of Clauses 7.2 and 7.4 were ruled.

3 Claim 'This survival translates into a substantial advantage for effectiveness in cost-effectiveness analysis'

This claim immediately followed that at issue in point A2 above.

COMPLAINT

Gilead Sciences alleged that the claim did not identify the product to which Vfend had been compared and thus was a hanging comparison which was misleading in breach of Clause 7.2.

Additionally at present, no definitive publication or analysis had been conducted to demonstrate that a 12-week survival improvement resulted in a 'substantial' advantage in cost. Gilead Sciences thus alleged that this was an exaggerated claim which could not be substantiated in breach of Clauses 7.4 and 7.10.

Gilead Sciences noted that in intercompany correspondence Pfizer had stated that the claim was part of the discussion around the comparative survival data and referred to a comparison of Vfend and amphotericin B. Pfizer had also stated that this claim made no cost-effectiveness claim but simply showed an effectiveness benefit as seen in clinical trials. Despite the fact that the claim at issue appeared in the part of the discussion around the comparative survival data Gilead Sciences considered that the claim itself could not stand alone. Additionally, as Pfizer had not stated the type of 'effectiveness' to which a substantial advantage was obtained, one was left to believe it was a cost advantage on the basis that it referred to cost-effectiveness analyses. Gilead Sciences therefore alleged a breach of Clauses 7.2, 7.4 and 7.10.

Gilead Sciences was concerned that no formal pharmacoeconomic model had been used to assess the value of Vfend in terms of cost-effectiveness, nor had any head-to-head study been conducted to formally evaluate the economic savings claimed through the use of Vfend in place of conventional amphotericin B in clinical practice. Therefore this advertorial did not appear to comply with the ABPI's Guidance on Good Practice in the Conduct of Economic Evaluations of Medicines which was recommended under Clause 7.2 of the Code (although it was not mandatory).

RESPONSE

Pfizer noted that the claim at issue was the third sentence of the third paragraph of the third section of the advertorial. It was clearly not intended to be considered in isolation. The preceding sentence described the source of data (including a mention of the comparator – initial treatment with amphotericin B) for the efficacy advantage and gave the appropriate study reference. The sentence commenced with 'This survival …' so clearly related to the data and study mentioned in the previous sentence. Additionally, a 12 percent survival benefit over 12 weeks was a substantial and significant effectiveness advantage in the context of invasive aspergillosis infections.

In relation to the claim at issue and those at issue at points A4 and A5 below Pfizer stressed the importance of considering the advertorial in its entirety, and not isolating individual sentences and attempting to take them out of the intended context. The advertorial postulated that the efficacy advantages that had been observed with Vfend in Herbrecht *et al* were likely to lead to a favourable cost-effectiveness ratio.

Pfizer acknowledged that the wording around the potential economic evaluations could have been clearer, and because of this had agreed to Gilead Sciences' request to include a paragraph regarding economic evaluations in the letter of clarification. However, Pfizer denied that the advertorial constituted a breach of the Code on these points.

PANEL RULING

The Panel noted that the claim at issue immediately followed the claim considered in point A2 above which compared Vfend and amphotericin B in relation to efficacy and improvement in survival. The claim at issue then began 'This *survival* …' (emphasis added), thus clearly referring to the comparison in the preceding sentence. The Panel thus did not consider that the claim was a hanging comparison as alleged. No breach of Clause 7.2 was ruled on this point.

The Panel noted that the supplementary information to Clause 7.2, economic evaluation of medicines stated, *inter alia*, that care must be taken that any claim involving the economic evaluation of a medicine was borne out by the data available and did not exaggerate its significance. Pfizer had not submitted a pharmacoeconomic evaluation in support of the claim.

The Panel acknowledged the difficulty of treating systemic fungal infections. Such infections were associated with a high mortality rate. Pfizer submitted that the 12 percent survival benefit over 12 weeks was a substantial and significant effectiveness advantage in the context of treating invasive

aspergillosis infections. The Panel considered that whilst a 12 percent survival benefit over 12 weeks would have cost implications no data had been provided to substantiate this point. Pfizer had stated that the advertorial postulated that the efficacy advantages for Vfend observed by Herbrecht *et al* were *likely* (emphasis added) to lead to a favourable cost effectiveness ratio. The claim at issue, however, implied that a formal pharmacoeconomic evaluation had been undertaken which had shown a cost effectiveness advantage for Vfend versus amphotericin B; that was not so. The claim was incapable of substantiation, misleading and exaggerated as alleged. Breaches of Clauses 7.2, 7.4 and 7.10 were ruled.

4 Claim 'Voriconazole is likely to reduce overall cost as well'

COMPLAINT

Gilead Sciences alleged that the claim implied that Vfend could potentially reduce overall cost in comparison to another agent. Neither a comparator product nor appropriate reference was cited. Gilead Sciences alleged that this sweeping statement was not capable of substantiation in breach of Clause 7.4 of the Code.

Gilead Sciences noted its general comments about pharmacoeconomic claims at point A3 above.

In intercompany correspondence Pfizer had stated that the sentence directly beneath the claim at issue highlighted that this related to a comparison of Vfend and liposomal amphotericin B or caspofungin. This was misleading since the claim must be clearly substantiated, not by implied substantiation. Gilead Sciences was currently unaware of any comparative pharmacoeconomic studies to support this claim, and indeed MIMS was cited as a reference. MIMS listed unit price and dose and did not consider overall costs as in a clinical setting. Thus this claim was misleading and could not be substantiated in breach of Clause 7.4 of the Code.

RESPONSE

Pfizer noted that the sentence directly following the claim at issue demonstrated that the daily cost for IV treatment was lower for Vfend than for liposomal amphotericin B or caspofungin, citing MIMS as an example of daily IV cost. The paragraph continued to highlight the potential cost benefits of an oral formulation of Vfend, while clearly there was no such oral formulation of either amphotericin B or caspofungin. Hence, given the qualification 'likely' in the claim, it was substantiable, and was clearly speculative in tone rather than affirmative.

Pfizer also noted its general comments about pharmacoeconomic claims at point A3 above.

PANEL RULING

The Panel noted that the claim at issue began, and would thus be considered in the context of, a paragraph which described how Vfend might reduce costs and which included a comparison with amphotericin B and caspofungin. The Panel did not consider that the claim 'Voriconazole is likely to reduce overall costs as well' implied that Vfend could potentially reduce overall cost in comparison to another unidentified agent as alleged. No breach of Clause 7.4 was thus ruled on this narrow point.

The Panel noted Gilead's allegation that there were no pharmacoeconomic studies to support the claim. MIMS was cited as a reference to the claim 'Daily drug cost for IV treatment is lower compared with liposomal amphotocin B or caspofungin' which immediately followed the claim at issue. The paragraph also mentioned the financial savings which accrued from length of hospital stay. The Panel considered that the claim at issue was speculative; stating that Vfend was *likely* to reduce overall costs (emphasis added) did not negate the impression that it *would* reduce costs. This impression was compounded by the cost savings discussed in the paragraph which referred, *inter alia*, to substantial financial savings. No data, other than medicine acquisition costs, had been provided to substantiate the claim 'Voriconazole is likely to reduce overall cost as well'. The claim was speculative and not capable of substantiation; a breach of Clause 7.4 was ruled.

5 Claim 'Consideration of cost-effectiveness principles reveals that initial treatment with voriconazole may offer not only a substantial efficacy advantage, but also a favourable cost benefit'

COMPLAINT

Gilead Sciences stated that the claim lacked definition as to the product with which a comparison was made and additionally provided no quantification for the 'substantial efficacy advantage'. Gilead Sciences alleged a breach of Clause 7.2. Furthermore Gilead Sciences alleged that this sweeping statement was not capable of substantiation in breach of Clause 7.4 of the Code.

Gilead Sciences noted its general comments about pharmacoeconomic claims at point A3 above.

In intercompany correspondence Pfizer had stated that this claim was intended to refer to previous information earlier in the advertorial and that it was not an absolute statement but merely postulated – referring to the principles of cost-effectiveness and the fact that there might be an efficacy and cost benefit. Pfizer had however accepted that this claim could have been clearer. Therefore, on the basis that it was not clear in the advertorial itself and that the claim was not capable of substantiation, Gilead Sciences alleged a breach of Clauses 7.2 and 7.4.

RESPONSE

Pfizer noted that this claim appeared in the paragraph which concluded the advertorial and therefore referred to the information contained within. It was clearly speculative in tone, referring to '… cost-effectiveness *principles* …' (emphasis added) and stated that '… voriconazole *may* offer …' (emphasis added).

Pfizer also noted its general comments about pharmacoeconomic claims at point A3 above.

PANEL RULING

The Panel noted that the claim at issue began the final paragraph of the article which summarized points raised therein. The Panel did not consider that it was incapable of substantiation because the comparator product was not identified as alleged; it was not a comparative claim. It summarized the points raised in the article and wherein comparators were identified. No breach of Clause 7.2 was ruled on this narrow point.

In relation to the allegation that it was a sweeping claim incapable of substantiation the Panel considered that its comments and rulings at points A3 and A4 were relevant. The Panel noted the speculative nature of the claim. The Panel considered that to state something may happen rarely negated the impression that it would happen. The Panel considered that the claim was misleading and incapable of substantiation as alleged. Breaches of Clauses 7.2 and 7.4 of the Code were ruled.

B Letter to UK recipients of the International Review of Patient Care

COMPLAINT

Gilead Sciences stated that on Monday, 7 February 2005, it received multiple copies of the letter sent by Pfizer which attempted to address the errors made within the advertorial considered at point A above. The letter however only addressed one of the many claims to which Gilead Sciences expressed unease and was distributed to a wider audience than had received the International Review of Patient Care 2005.

Although the letter attempted to clarify the time period for which a potential benefit in survival was seen with Vfend, the final paragraph made a further claim. Gilead Sciences understood that the purpose of the letter was primarily to provide clarity for health professionals and was most definitely not a promotional opportunity for Pfizer. However the following statement which formed the last paragraph of the letter was of particular interest: 'The article goes on to postulate that this survival benefit at 12 weeks is a substantial efficacy benefit which may also translate into a favourable cost-effectiveness benefit compared to other licensed antifungal agents. This work however has yet to be undertaken'.

This statement suggested that despite the fact that no definitive study or trial had been conducted to specifically investigate the efficacy or cost-effectiveness advantage of Vfend on the basis of the 12 week survival benefit, one could postulate that this would be substantial. Gilead Sciences considered therefore that on the basis that this statement was unsubstantiated, was not a fair representation of available evidence and was misleading by implication, it was in breach of Clauses 7.2 and 7.4.

RESPONSE

Pfizer denied a breach of the Code. Pfizer and Gilead Sciences had agreed that withdrawal of material from circulation was unlikely to be effective. As a compromise, it was agreed that a letter of clarification should be sent to the UK recipients of the International Review of Patient Care 2005. Having initially agreed that the editor of that publication could send the letter, Gilead Sciences later requested that Pfizer sent it. It was also agreed that Pfizer would draft a letter and send it to Gilead Sciences for its comment, input and approval prior to the letter being sent to the distribution list. The possibility of a teleconference or meeting was also raised to facilitate agreement on wording of the letter. Pfizer acted in line with the agreement and drafted a letter, which was sent to Gilead Sciences. Gilead Sciences stated verbally that it was not satisfied with the letter but did not offer any suggestions for changes. It offered no feedback or input at all, and simply stated that it was going to make a formal complaint.

The letter emphasised that the survival benefit was seen as 12 weeks. It also made clear the fact that the cost-effectiveness work had yet to be undertaken. 'The article goes on to postulate that this survival benefit at 12 weeks is a substantial efficacy benefit which may also translate into a favourable cost-effectiveness benefit compared to other licensed anti-fungal agents. This work, however, has yet to be undertaken'.

Pfizer denied Gilead Sciences' claim that the statement suggested a substantial cost-effectiveness advantage of Vfend; this was a blatant misreading of the statement.

Pfizer noted that the statement actually stated that the survival benefit at 12 weeks with Vfend was a substantial *efficacy* benefit. No attempt was made to quantify or qualify any potential cost-effectiveness benefit. Indeed the statement stated that '… benefit which may also translate …' so the possibility of an unfavourable cost-effectiveness benefit was not excluded.

PANEL RULING

The Panel noted that the penultimate paragraph of the letter read 'The article goes on to postulate that this survival benefit at 12 weeks is a substantial efficacy benefit which may also translate into a favourable cost-effectiveness benefit compared to other licensed anti fungal agents. This work, however, has yet to be undertaken'. The Panel noted that whilst the letter stated clearly that the work to substantiate the claim had yet to be undertaken such a caveat did not negate the overriding impression that a favourable cost effectiveness benefit would be achieved. There was however no evidence to substantiate the impression given. Speculation was not an acceptable basis for claims. To claim that something *may* happen rarely negated the impression that it would. The Panel considered the statement misleading and incapable of substantiation as alleged. Breaches of Clauses 7.2 and 7.4 were ruled.

C Clause 2

COMPLAINT

Gilead Sciences stated that Pfizer's behaviour in relation to this matter was of grave concern. Not only

had it breached the Code by making misleading claims in the advertorial, it had gone against an intercompany agreement made in good faith, and widely distributed a clarification letter making further misleading claims. Pfizer admitted that the advertorial was placed without the knowledge of the UK company and this lack of adequate internal control systems within the company also caused concern. Pfizer's actions in this case served not only to undermine the level of confidence and trust that health professionals had in pharmaceutical companies to comply with the Code by providing them with accurate and factually correct information but also reduced their confidence in the enforcement of rulings made under the Code. By wilfully ignoring an intercompany agreement Pfizer could only undermine the level of trust between companies within the industry. Gilead Sciences considered very strongly that Pfizer's behaviour constituted a most serious breach of the Code, that of bringing discredit to and reducing confidence in the pharmaceutical industry. A breach of Clause 2 of was alleged.

RESPONSE

Pfizer did not respond on this point.

PANEL RULING

The Panel noted its comments and rulings at point A2 above in relation to the breach of undertaking; including a ruling of a breach of Clause 2. The Panel considered that the allegations about the claims in the advertorial and comment on the company's policies and procedures were covered by its ruling at point A2 above. The Panel did not consider that any points additional to the breach of undertaking warranted a further ruling of a breach of Clause 2 which was reserved as a sign of particular censure. No breach of Clause 2 was thus ruled.

* * * * *

During its consideration of this case the Panel noted that the advertisement at issue, in the form of an advertorial, was part of a double page spread. It was published alongside a traditional advertisement for Vfend. The Panel considered that the presentation and style of each page was so different that they were designed to be read as separate pages rather than as one double page spread. In the Panel's view the advertorial was a standalone advertisement for Vfend and therefore required prescribing information. The Panel further noted that the advertorial did not have the word(s) 'advertisement' or 'advertisement feature' at the top. In the Panel's view even with these words at the top the advertorial might still have been regarded as disguised promotion if its general appearance and layout was similar to that of the editorial of the International Review of Patient Care. The Panel did not have a copy of that publication before it to compare the two and to see if there was adequate differentiation. The Panel requested that Pfizer be advised of its views.

Complaint received **11 February 2005**

Case completed **19 April 2005**

CASE AUTH/1678/2/05

MEMBER OF THE PUBLIC v BOEHRINGER INGELHEIM

Activities of representatives

A complaint was received that contract representatives working for Boehringer Ingelheim were calling on doctors more frequently than allowed under the Code.

The complainant stated that the contract representative agency positively encouraged, by way of a bonus of around £1,000, overly frequent calls in order to achieve coverage on their list of target general practitioners from Boehringer Ingelheim. The complainant noted that representative V called on doctor X on 3 and 5 November, 9, 15 and 20 December, 17 and 28 January and 10 February; representative W called on doctor Y on 1, 5, 16 and 19 November and called on doctor Z on 1 and 4 November, 10, 16 and 24 December and 7 January. The complainant alleged a breach of the Code and considered that such unethical behaviour was likely to bring the pharmaceutical industry into disrepute.

The Panel was concerned that the call data provided for representative V and doctor X showed that in the 14 weeks from 3 November 2004 to 10 February 2005 there had been eight calls: one planned call; four planned meetings; two meetings arranged at short notice at the request of the practice, and one call to deliver a promotional aid. The Panel was surprised that the representative agreed to cover two meetings at short notice, as each time she had a meeting of her own planned at the surgery within the next week. The Panel noted that the three allowable unsolicited visits that a representative could normally make throughout a year were to be made in a whole year. The complaint, however, concerned a 14 week time period wherein the representative had only made one planned call; all other contacts with doctor X and/or the surgery had been requested or had been educational meetings. Whilst the Panel was concerned about the intervals between successive visits, on balance, it decided to rule no breach of the Code.

With regard to representative W's contact with doctor Y, the Panel noted that three calls had been made within 3 weeks. Boehringer Ingelheim had no record of a call which the complainant alleged took place on 5 November. The first and second calls made by the representative appeared to be unsolicited and the third, three days after the second, was in response to a request to discuss sponsorship of a meeting. The representative had made two unsolicited calls in just over a fortnight. The Panel considered that this was excessive frequency and thus ruled a breach of the Code. High standards had not been maintained. A breach of the Code was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code.

With regard to representative W's contact with doctor Z, the Panel noted that six calls had been made to the doctor and/or surgery within a 10 week period. One call had been a meeting, four had been planned and one had been in response to a request to deliver a promotional aid. The Panel noted that the representative had planned to see doctor Z on 4 November and 24 December. In addition on two occasions (16 December and 7 January) when the representative had called to see another doctor she had, opportunistically, also seen doctor Z who initiated a conversation with her whilst she was in the practice. The Panel considered that such frequency of unsolicited calls on both doctors was excessive and thus ruled a breach the Code. High standards had not been maintained a breach of the Code was ruled. The Panel did not consider that the circumstances warranted a ruling of a Clause 2 of the Code.

A complaint was received about the activities of contract representatives working for Boehringer Ingelheim Limited. The supplementary information to Clause 15 of the Code provided that companies employing or using contract representatives were responsible for their conduct and compliance with the Code. Boehringer Ingelheim was thus responsible for the activities of the representatives.

COMPLAINT

The complainant stated that the company appeared to be not only ignoring, but positively encouraging overly frequent calls on general practitioners. The complainant provided the following examples of multiple calls in a short space of time:

- Representative V called on doctor X on 3 and 5 November, 9, 15 and 20 December, 17 and 28 January and 10 February.
- Representative W called on doctor Y on 1, 5, 16 and 19 November and called on doctor Z on 1 and 4 November, 10, 16 and 24 December and 7 January.

The complainant stated that these calls by the contract representatives were in addition to those from the client companies.

The complainant alleged that the contract representative agency had encouraged its representatives to make these frequent calls in order to achieve coverage on their list of target general practitioners from Boehringer Ingelheim. The complainant understood that this was rewarded last year by some representatives receiving a bonus of around £1,000.

The complainant alleged a breach of Clause 15.4 of the Code and considered that such unethical behaviour was likely to bring the pharmaceutical industry into disrepute.

When writing to Boehringer Ingelheim, the Authority asked it to respond in relation to Clauses 9.1 and 2 in addition to Clause 15.4 cited by the complainant.

RESPONSE

Boehringer Ingelheim stated that the contract representative agency had investigated the specific call data, and considered that there were mitigating circumstances in relation to the frequency of calling,

which were covered in the call comments in a spreadsheet which was provided. The doctors or practice staff requested many of the contacts and there was no indication from any member of staff that the contacts had caused offence, nuisance or inconvenience. In addition to this, several calls at the practice were to see other doctors, other members of staff or nurses when an opportunistic contact was made with the doctor in question through a conversation that was not initiated by the representative.

The contract representative agency considered that it had observed the wishes of all individuals whom its representatives had called on and had observed the arrangements in force at these practices for calling on individuals within them. The company submitted that its representatives had a good relationship with these practices; the contract representative agency was sure that the practices would testify to this if required.

Boehringer Ingelheim noted that with regard to the generalised claim, the contract representative agency had provided copies of the sales representatives' incentive scheme. The contact frequency on target doctors between August and December 2004 (which formed part of the individual objectives) was 2.7 times by 50 representatives on 80 doctors and 2 times by 20 representatives on 80 doctors. With regard to bonusing the contract representative agency stated that its representatives were paid a salary that was comparable with the average salary for medical representatives in the industry. In addition they also participated in an incentive scheme that was made up of sales, call rate and general behavioural standards.

During the period August 2004 and December 2004 the sales team in question was incentivised to achieve a set territory call rate/volume, a sales target for one product and minimum standards in the call reporting system. The payment for an 'on target' achievement of all parameters was £1,000. This was not linked exclusively to call rates. The bonus payment of £1,000 in the six-month period represented 3.8% of salary, the average salary in the team being £26,000. The contract representative agency considered that this complied with Clause 15.7 as it did not constitute an undue proportion of the representatives' remuneration.

Boehringer Ingelheim stated that there was no additional incentive or reward or direction given to the representatives to achieve higher frequencies than those quoted.

Boehringer Ingelheim stated that the targeting of GPs by representatives was an evolving process through the year to achieve appropriate coverage of target doctors without wasting representative resource either by under or overcalling. It was designed around a framework which aimed for a maximum annual target average of three calls plus contacts at meetings or requested calls, in line with the supplementary information to Clause 15.4. Thus, the 2.7 contacts target for August to the end of December could not be simply extrapolated to give a twelve month contact rate.

In relation to Clause 9.1 Boehringer Ingelheim stated that the contract representative agency had noted that as a service organisation it prided itself on the quality of representative it recruited, trained and developed. To this end, each of its representatives underwent extensive training (including training on the Code) and ongoing development. One of these training interventions involved its representatives being assessed by GPs for their skills and approach to seeing customers. The representatives were then given direct feedback by the GPs to aid their understanding of the real needs of NHS customers. This on going training and benchmarking happened twice a year and representatives were expected to score higher than the industry average. Both of the representatives concerned had scored above industry average in their assessments by GPs.

Boehringer Ingelheim stated that the contract agency provided it with the representatives' services under contract. This contract included the potential for a bonus to be paid to the representative but did not dictate its content, which would be influenced by arrangements with other pharmaceutical companies. The manner in which these calls were to be made was covered in the contract under Schedule 1 which stated: '[the contract representative agency] shall ensure that [its dedicated staff] are familiar with the provisions of the [Code] and shall use its reasonable endeavours to ensure compliance by all [dedicated staff] with its provisions and shall provide appropriate training assistance'.

Boehringer Ingelheim stated that, in summary, the contract representative agency had provided evidence that suggested not only that no breach of Clauses 15.4 or 9.1 took place in the specific example provided, but that no breach of Clauses 15.4, 9.1 or 2 had taken place in the targeting or bonusing of the contract representatives.

PANEL RULING

The Panel noted that Clause 15.4 of the Code stated, *inter alia*, that representatives must ensure that the frequency, timing and duration of calls on health professionals, administrative staff in hospitals and health authorities and the like, together with the manner in which they were made, did not cause inconvenience. The supplementary information to Clause 15.4 stated, *inter alia*, that the number of calls made on a doctor and the intervals between successive visits were relevant to the determination of frequency. The number of calls made on a doctor by a representative each year should not normally exceed three on average. This did not include attendance at group meetings, a visit requested by a doctor or a call made to respond to a specific enquiry or a visit to follow up a report of an adverse reaction, all of which were additional to the three visits.

The Panel was concerned about call data provided by the contract representative agency. The data for representative V and doctor X showed that in the 14 weeks from 3 November 2004 to 10 February 2005 there had been eight calls: one planned call; four planned meetings; two meetings arranged at short notice at the request of the practice, and due to another representative cancelling, and one call to deliver a promotional aid. The Panel was surprised

that the representative agreed to cover an evening meeting and a lunchtime meeting, both at short notice, despite, each time, having a meeting of her own planned at the surgery within the next week. The Panel noted the requirements of Clause 15.4 and the guidance given in the relevant supplementary information. The Panel noted that the three allowable unsolicited visits that a representative could make throughout a year were to be made in a whole year. The complaint, however, concerned a 14 week time period wherein the representative had only made one planned call; all other contacts with doctor X and/or the surgery had been requested or had been educational meetings. Whilst the Panel was concerned about the intervals between successive visits on balance it decided to rule no breach of Clause 15.4. There was thus no breach of Clauses 2 and 9.1 and so the Panel ruled accordingly.

With regard to representative W's contact with doctor Y, the Panel noted that three calls had been made within 3 weeks. Boehringer Ingelheim had no record of a call which the complainant alleged took place on 5 November. The first and second calls made by the representative appeared to be planned and unsolicited and the third call, three days after the second, was in response to a request to discuss sponsorship of a meeting. The Panel noted the requirements of Clause 15.4 and the guidance given in the relevant supplementary information. The representative had made two unsolicited calls in just over a fortnight. The Panel considered that this was excessive frequency and thus ruled a breach of Clause 15.4 of the Code. High standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was reserved as a sign of particular censure.

With regard to representative W's contact with doctor Z, the Panel noted that six calls had been made to the doctor and/or surgery within a 10 week period. One call had been a meeting, four calls had been planned and one had been in response to a request to deliver a promotional aid. The Panel noted that the representative had planned to see doctor Z on 4 November and 24 December. In addition on two occasions (16 December and 7 January) when the representative had called to see another doctor she had, opportunistically, also seen doctor Z who initiated a conversation with her whilst she was in the practice. The Panel considered that such frequency of unsolicited calls on both doctors was excessive and thus ruled a breach of Clause 15.4 of the Code. High standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel did not consider that the circumstances warranted a ruling of a Clause 2 of the Code.

During its consideration of this case the Panel was concerned to note Boehringer Ingelheim's submission that some of the contract agency representatives had been given a target contact frequency on target doctors between August and September 2004 of 2.7 times whilst other representatives had been given a target of 2 for the same time period. The Panel noted the requirements of Clause 15.4 with regard to frequency of calls. The Panel also noted that the three allowable unsolicited visits that a representative could make throughout a year were to be made in a whole year. A company could not instruct its representatives to visit a doctor three times during August to December of one year and then another three times in the whole of the next calendar year. The Panel requested that Boehringer Ingelheim be advised of its concerns in this regard.

Complaint received **14 February 2005**

Case completed **17 May 2005**

CASE AUTH/1679/2/05

MEMBER OF THE PUBLIC v NOVARTIS

Activities of representatives

A complaint was received that contract representatives who had worked for Novartis were calling on doctors more frequently than allowed under the Code.

The complainant stated that the contract representative agency positively encouraged, by way of a bonus of around £1,000, overly frequent calls in order to achieve coverage on their list of target general practitioners from [a named pharmaceutical company]. The complainant noted that representative V called on doctor X on 3 and 5 November, 9, 15 and 20 December, 17 and 28 January and 10 February; representative W called on doctor Y on 1, 5, 16 and 19 November and called on doctor Z on 1 and 4 November, 10, 16 and 24 December and 7 January. The complainant alleged a breach of the Code and considered that such unethical behaviour was likely to bring the pharmaceutical industry into disrepute.

The Panel was concerned that the call data for representative V and doctor X showed that in the 14 weeks from 3 November 2004 to 10 February 2005 there had been eight calls: one planned speculative call; four planned meetings; two meetings arranged at short notice at the request of the practice manager, and one call to deliver a promotional aid. The Panel was surprised that the representative agreed to cover two meetings at short notice, as each time she had a meeting of her own planned at the surgery within the next week. The Panel noted that the three allowable unsolicited visits that a representative could normally make throughout a year were to be made in a whole year. The complaint however concerned a 14 week time period wherein the representative had only made one planned call; all other contacts with doctor X and/or the surgery had been requested or had been educational meetings. Whilst the Panel was concerned about the intervals between successive visits, on balance, it decided to rule no breach the Code.

With regard to representative W's contact with doctor Y, the Panel noted that three calls had been made within 3 weeks. The Panel noted Novartis' submission that although recorded, no call took place on 5 November. The first and second calls made by the representative appeared to be unsolicited and the third, three days after the second, was in response to a request to discuss sponsorship of a meeting. The representative had made two unsolicited calls in just over a fortnight. The Panel considered that this was excessive frequency and thus ruled a breach of the Code. High standards had not been maintained a breach of the Code was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code.

With regard to representative W's contact with doctor Z, the Panel noted that six calls had been made to the doctor and/or surgery within a 10 week period. One call had been a group meeting, four had been planned speculative calls and one had been in response to a request to deliver a promotional aid. The Panel noted that the representative had planned to see doctor Z on 4 November and 24 December. In addition on two occasions (16 December and 7 January) when the representative had called to see another doctor she had opportunistically also seen doctor Z who initiated a conversation with her whilst she was in the practice. The Panel considered that such frequency of unsolicited calls was excessive and thus ruled a breach of the Code. High standards had not been maintained and a breach of the Code was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code.

A complaint was received about the activities of contract representatives who had worked for Novartis Pharmaceuticals UK Ltd since October 2004. The supplementary information to Clause 15 of the Code provided that companies employing or using contract representatives were responsible for their conduct and compliance with the Code. Novartis was thus responsible for the activities of the representatives.

COMPLAINT

The complainant stated that the company appeared to be not only ignoring, but positively encouraging overly frequent calls on general practitioners. The complainant provided the following examples of multiple calls in a short space of time:

- Representative V called on doctor X on 3 and 5 November, 9, 15 and 20 December, 17 and 28 January and 10 February.
- Representative W called on doctor Y on 1, 5, 16 and 19 November and called on doctor Z on 1 and 4 November, 10, 16 and 24 December and 7 January.

The complainant stated that these calls by the contract representatives were in addition to those from the client companies.

The complainant alleged that the contract representative agency had encouraged its representatives to make these frequent calls in order to achieve coverage on their list of target GPs from [a named pharmaceutical company]. The complainant understood that this was rewarded last year by some representatives receiving a bonus of around £1,000.

The complainant alleged a breach of Clause 15.4 of the Code and considered that such unethical behaviour was likely to bring the pharmaceutical industry into disrepute.

When writing to Novartis, the Authority asked it to respond in relation to Clauses 9.1 and 2 in addition to Clause 15.4 as cited by the complainant.

RESPONSE

Novartis submitted that according to the contract representative agency many of the calls referred to by the complainant were made at the request of

customers, as well as follow up calls and group meetings as opposed to unsolicited calls. A spreadsheet with comments provided by the contract agency regarding the nature of the calls made by the two representatives was provided.

Novartis noted that the complainant alleged that representative V saw doctor X eight times between November 2004 and February 2005. The comments logged by the contract representative agency against each of those calls indicated that:

– one was unsolicited

– four were group meetings

– two were nurse meetings to which the GP in question was not invited, but attended of their own accord

– one was to deliver a requested item

Novartis noted the complainant had alleged that representative W saw doctor Y four times in November 2004 and saw doctor Z six times between November 2004 to January 2005. The comments logged against the calls made to doctor Y indicated that:

– one was unsolicited

– one was entered by mistake when in fact no call took place

– two were requested by the customers.

The comments logged against the calls made to doctor Z indicated that:

– two were unsolicited

– two were group meetings

– one was to deliver a requested item

– two made were to see another doctor within the practice, but doctor Z initiated discussions with the representative on both occasions.

Although each of the two representatives had made two or less unsolicited calls to each of the three doctors in question during this time period, they did not make any further unsolicited calls to these doctors during the twelve month period and therefore had adhered to the requirements of the Code. Furthermore statements provided by the two representatives in relation to the alleged calls confirmed that the doctor or practice staff requested many of these calls, and there was no indication from any member of staff that the calls were causing offence or nuisance.

Novartis did not consider that the representatives in question had breached Clause 15.4 of the Code as they did not exceed three unsolicited calls in a year. Novartis was satisfied that the contacts made by the representatives did not cause inconvenience to the GPs in question and were in accordance with the Code.

The representatives were paid a salary that was comparable with the average salary paid to medical representatives in the industry. In addition to this they participated in an incentive scheme that was made up of sales, call rate and general behavioural standards. The contract representative agency had stated that during the period August 2004 and December 2004, the representatives were incentivised to achieve a set territory call rate/volume, a sales target for one product and achieve minimum standards in call reporting and administrative duties. The payment for an 'on target' achievement of all parameters was £1,000. This was not linked exclusively to call rates but also linked to sales target, general behaviour standards and administrative duties. The bonus payment of £1,000 in the six-month period represented 3.8% of salary, the average salary in the team being £26,000. Novartis considered that this was in accordance with the Code as it did not constitute an undue proportion of the representatives' remuneration.

Novartis strongly denied that the contract representatives working for the company were encouraged to make unacceptable frequent calls in order to achieve coverage of Novartis target customers. The Novartis sales force worked to high professional standards and expected the same for all contracted sales representatives.

Novartis did not consider that this activity represented breaches of Clause 15.4, 9.1 or indeed Clause 2 of the Code.

PANEL RULING

The Panel noted that Clause 15.4 of the Code stated, *inter alia*, that representatives must ensure that the frequency, timing and duration of calls on health professionals, administrative staff in hospitals and health authorities and the like, together with the manner in which they were made, did not cause inconvenience. The supplementary information to Clause 15.4 stated, *inter alia*, that the number of calls made on a doctor and the intervals between successive visits were relevant to the determination of frequency. The number of calls made on a doctor by a representative each year should not normally exceed three on average. This did not include attendance at group meetings, a visit requested by a doctor or a call made to respond to a specific enquiry or a visit to follow up a report of an adverse reaction, all of which were additional to the three visits.

The Panel was concerned about call data provided by the contract representative agency. The data for representative V and doctor X showed that in the 14 weeks from 3 November 2004 to 10 February 2005 there had been eight calls: one planned speculative call; four planned meetings; two meetings arranged at short notice at the request of the practice manager, due to another representative cancelling and one call to deliver a promotional aid. The Panel was surprised that the representative agreed to cover an evening meeting and a lunchtime meeting, both at short notice, despite, each time, having a meeting of her own planned at the surgery within the next week. The Panel noted the requirements of Clause 15.4 and the guidance given in the relevant supplementary information. The Panel noted that the three allowable unsolicited visits that a representative could make throughout a year were to be made in a whole year. The complaint however concerned a 14 week time

period wherein the representative had only made one planned call; all other contacts with doctor X and/or the surgery had been requested or had been educational meetings. Whilst the Panel was concerned about the intervals between successive visits on balance it decided to rule no breach of Clause 15.4. There was thus no breach of Clauses 2 and 9.1 and so the Panel ruled accordingly.

With regard to representative W's contact with doctor Y, the Panel noted that three calls had been made within 3 weeks. The Panel noted Novartis' submission that although recorded, no call took place on 5 November. The first and second calls made by the representative appeared to be planned and unsolicited and the third call, three days after the second, was in response to a request to discuss sponsorship of a meeting. The Panel noted the requirements of Clause 15.4 and the guidance given in the relevant supplementary information. The representative had made two unsolicited calls in just over a fortnight. The Panel considered that this was excessive frequency and thus ruled a breach of Clause 15.4 of the Code. High standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was reserved as a sign of particular censure.

With regard to representative W's contact with doctor Z, the Panel noted that six calls had been made to the doctor and/or surgery within a 10 week period. One call had been a group meeting, four calls had been planned speculative calls and one had been in response to a request to deliver a promotional aid. The Panel noted that the representative had planned to see doctor Z on 4 November and 24 December. In addition on two occasions (16 December and 7 January) when the representative had called to see another doctor she had opportunistically also seen doctor Z who initiated a conversation with her whilst she was in the practice. The Panel considered that such frequency of unsolicited calls was excessive and thus ruled a breach of Clause 15.4 of the Code. High standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel did not consider that the circumstances warranted a ruling of a no breach of Clause 2 of the Code.

During its consideration of this case the Panel noted the requirements of Clause 15.4 of the Code with regard to frequency of calls; the three allowable unsolicited visits that a representative could make throughout a year were to be made in a whole year. A company could not instruct its representatives to visit a doctor three times between August and December of one year and then another three times in the whole of the next calendar year. The Panel requested that Novartis be reminded of the Code's requirements in this regard.

Complaint received **14 February 2005**

Case completed **23 May 2005**

CASE AUTH/1680/2/05 *NO BREACH OF THE CODE*

GENERAL PRACTITIONER v NOVARTIS

Diovan mailing

A general practitioner complained about a Diovan (valsartan) mailing sent by Novartis entitled 'Could Diovan help more of your patients reach target?'. A downward arrow on one page of the mailing showed the percentage of hypertensive patients achieving target blood pressure with 'Diovan-based therapy*'. The asterisk led to a footnote which read 'Diovan 80-160mg +/- 1 other drug (n=18,544)'. A claim below the arrow stated 'Diovan-based therapy brings over 70% of hypertensive patients to the [General Medical Services] GMS Contract target of ≤ 150/90mmHg' and was referenced to data on file.

The complainant alleged that the wording was inappropriate and the presentation of the data potentially misleading. Valsartan was an angiotensin-II receptor antagonist. Neither the National Institute for Clinical Excellence (NICE) nor the British Hypertension Society (BHS) recommended this group of medicines as first-line management of hypertension. The complainant alleged that the phrase 'Diovan-based therapy' was inappropriate, since Diovan in general should be used as an add-on medicine. A brief glance at the page with the downward arrow gave the impression that Diovan was being used on its own, whereas the cited trial included many patients who were on Diovan plus another medicine.

The Panel noted that according to its summary of product characteristics (SPC) Diovan was licensed, *inter alia*, for the treatment of hypertension either as a monotherapy or in combination with other antihypertensives. The BHS guidelines (Williams *et al* 2004) did not recommend angiotension receptor blockers for the first-line treatment of older (≥ 55 years) or black patients with hypertension. NICE, in its clinical guideline on the management of hypertension in adults in primary care (August 2004), recommended that therapy should normally begin with a low-dose thiazide-type diuretic with other medicines being used as second line; patients at raised risk of new-onset diabetes should be prescribed an ACE inhibitor. The Panel considered that although NICE did not recommend angiotension receptor blockers as first-line agents, and the BHS only recommended them as first-line agents for some patients, Novartis was nonetheless entitled to promote Diovan as a first-line agent, within the terms of its marketing authorization. In the Panel's view the claim 'Diovan-based therapy' was consistent with the indication given in the Diovan SPC. The Panel thus did not consider that the mailing was misleading in that regard and no breach of the Code was ruled.

The Panel did not consider that the phrase 'Diovan-based therapy' implied that Diovan was being used on its own as alleged. In the Panel's view, it was clear that therapy was based on Diovan but did not necessarily consist of Diovan alone. Doctors would know that many hypertensives needed combination therapy to control their blood pressure. No breach of the Code was ruled.

A general practitioner complained about a Diovan (valsartan) mailing (ref DIO04777202) sent by Novartis Pharmaceuticals UK 'Could Diovan help more of your patients reach target?'. The one page of clinical data, headed 'Achieving today's targets with powerful BP control', featured a downward arrow showing the 'Percentage of hypertensive patients achieving [General Medical Services] GMS Contract target with Diovan-based therapy*'. The asterisk led the reader to a footnote which read 'Diovan 80-160mg +/- 1 other drug (n=18,544)'. A claim below the arrow stated 'Diovan-based therapy brings over 70% of hypertensive patients to the GMS Contract target of ≤ 150/90mmHg' and was referenced to data on file.

COMPLAINT

The complainant alleged that the wording of the leaflet was inappropriate and the presentation of the information potentially misleading. Valsartan was an angiotensin-II receptor antagonist. Neither the National Institute for Clinical Excellence (NICE) nor the British Hypertension Society (BHS) guidelines recommended this group of medicines as first-line management of hypertension. The complainant alleged that the phrase 'Diovan-based therapy' was inappropriate, since Diovan in general should be used as an add-on medicine in the management of hypertension.

The complainant stated that a brief glance at the page with the downward red arrow gave the impression that Diovan was being used on its own, whereas the cited trial included many patients who were on Diovan plus another medicine.

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

RESPONSE

Novartis submitted that the BHS recommended angiotensin receptor blockers as possible first-line treatment for hypertension in its most recent guidelines; its recommendation for combining antihypertensives, the AB/CD algorithm, stated that an ACE inhibitor or an angiotensin receptor blocker or a ß-blocker should be first-line treatment for hypertension in younger patients (eg <55 yrs) and non-black patients.

The NICE practice guidelines for essential hypertension (managing adult patients in primary care) recommended angiotensin receptor blockers as second-line/add-on treatment for hypertension (following thiazide diuretic treatment) in patients at higher risk of new-onset diabetes where ACE inhibitors were not tolerated. However, the NICE clinical guidelines for blood pressure management in type 2 diabetes recommended angiotensin receptor blockers as possible first-line antihypertensive therapy;

> 'Use ACE inhibitors, angiotensin II receptor antagonists, beta blockers or thiazide diuretics as first line treatments in those people without microalbuminuria.

> Use ACE inhibitors as the class of first choice in people with microalbuminuria or proteinuria. Where ACE inhibitors are unsuitable or are contraindicated in people with microalbuminuria or proteinuria, then angiotensin II receptor antagonists may be considered as alternative first line therapy'.

Novartis disagreed with the complainant's statement that in general, Diovan should be used as an add-on medicine in the management of hypertension so the phrase 'Diovan-based therapy' was inappropriate. Novartis noted that Diovan was licensed for the treatment of hypertension and was not restricted to add-on therapy nor treatment of hypertensive patients not controlled to target on other antihypertensives. Novartis further noted that the BHS guidelines and the NICE clinical guidelines for blood pressure management in type 2 diabetes recommended the use of angiotensin receptor blockers (eg Diovan) for first-line treatment of hypertension as discussed above.

Novartis noted that the definition of the phrase 'Diovan-based therapy' was immediately adjacent to the arrow head, ie, 'Diovan 80-160mg +/– 1 other drug'. Therefore, in the context of the mailing, the phrase, 'Diovan-based therapy', clearly represented Diovan monotherapy or Diovan in combination with another antihypertensive. Novartis provided a summary of the data on file used to support this claim, together with Schotze *et al* (2000) which was reanalysed as discussed in the data on file summary.

Novartis did not consider that the mailing inferred that the data was derived from studies of Diovan monotherapy. In fact it was repeatedly made clear that the data was sourced from a study where combination treatment was used.

Novartis denied a breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that according to its summary of product characteristics (SPC) Diovan was licensed, *inter alia*, for the treatment of hypertension either as a monotherapy or in combination with other antihypertensive agents. The BHS guidelines (Williams *et al* 2004) did not recommend angiotension receptor blockers for the first-line treatment of older (≥ 55 years) or black patients with hypertension. NICE, in its clinical guideline on the management of hypertension in adults in primary care (August 2004), recommended that therapy should normally begin with a low-dose thiazide-type diuretic with other medicines being used as second line; patients at raised risk of new-onset diabetes should be prescribed an ACE inhibitor. The Panel considered that although NICE did not recommend angiotension receptor blockers as first-line agents, and the BHS only recommended them as first line agents for some patients, Novartis was nonetheless entitled to promote Diovan as a first-line agent, within the terms of its marketing authorization.

The Panel noted that the difference between the indication given in the Diovan SPC and the guidance issued by the BHS and NICE appeared to have given rise to the complainant's concerns. In the Panel's view, however, the claim 'Diovan-based therapy' was consistent with the indication for Diovan given in its SPC. The Panel thus did not consider that the mailing was misleading in that regard. No breach of Clause 7.2 was ruled.

The Panel did not consider that the phrase 'Diovan-based therapy' implied that Diovan was being used on its own as alleged. In the Panel's view, it was clear that therapy was based on Diovan but did not necessarily consist of Diovan alone. Doctors would know that many hypertensive patients needed combination therapy to control their blood pressure. No breach of Clause 7.2 was ruled.

Complaint received **18 February 2005**

Case completed **31 March 2005**

CASE AUTH/1681/2/05

BOEHRINGER INGELHEIM v SANKYO PHARMA

Olmetec journal advertisements

Boehringer Ingelheim alleged that two journal advertisements for Olmetec (olmesartan), issued by Sankyo Pharma, which employed the wording 'There's nothing better....' as in 'There's nothing better to get Yvonne bang on' and 'There's nothing better to get Margaret to target' were in breach of the Code. The claims were ambiguous and misled the reader. The phrase 'There's nothing better…' was a hanging comparison as it did not clarify whether the claims referred to a comparison with: anything, pharmacological or otherwise, that was likely to lower blood pressure; all the currently available antihypertensive agents, irrespective of class; all of the other angiotensin II receptor antagonists (AIIAs) or a particular AIIA, such as Micardis (telmisartan marketed by Boehringer Ingelheim). Boehringer Ingelheim alleged that the claims were unsubstantiable, with respect to all of these points, were all-embracing and exaggerated the efficacy and safety of Olmetec in managing essential hypertension in breach of the Code.

The Panel did not consider that the claims 'There's nothing better to get Yvonne bang on' or 'There's nothing better to get Margaret to target' were hanging comparisons as alleged. In the context in which the claims appeared it was clear that the comparison was with all other antihypertensives. The Panel ruled no breach of the Code in that regard.

The Panel considered that the claims at issue implied that no other antihypertensive therapy/regimen was better than Olmetec at reducing patients' blood pressure to target. The claims did not exclude the possibility that another antihypertensive therapy/regimen might be equally efficacious. The Panel noted that Sankyo had referred to a number of studies to support the claims. These studies, however, did not include head-to-head trials of Olmetec versus every other antihypertensive therapy/regimen. The data supplied by Sankyo showed that Olmetec monotherapy had only been compared with monotherapy with three AIIAs, one beta-blocker, one ACE inhibitor and one calcium channel blocker. No data was provided comparing Olmetec with combination therapy. The Panel considered that the claims 'There's nothing better ...' were broad unequivocal claims which suggested that every other antihypertensive therapy/regimen had been compared with Olmetec and that none had been shown to be more efficacious. This was not so. The Panel considered in that regard that the claims were misleading, exaggerated and thus could not be substantiated. Breaches of the Code were ruled.

Boehringer Ingelheim Limited complained about two journal advertisements (refs OLMGA30501HCP and OLMPA30503HCP) for Olmetec (olmesartan medoxomil) issued by Sankyo Pharma UK Ltd which had appeared in GP and Pulse respectively. Correspondence between the parties had failed to resolve the matter.

COMPLAINT

Boehringer Ingelheim alleged that all of the current Olmetec promotional materials employing the wording 'There's nothing better....' such as 'There's nothing better to get Yvonne bang on' and 'There's nothing better to get Margaret to target' were in breach of the Code. The claims were ambiguous and misled the reader.

Boehringer Ingelheim alleged that the phrase 'There's nothing better…' was a hanging comparison as it did not clarify whether these claims referred to a comparison with: anything, pharmacological or otherwise, that was likely to lower blood pressure; all currently available antihypertensives, irrespective of class; all of the other angiotensin II receptor antagonists (AIIAs) or with a particular AIIA such as Micardis (telmisartan, marketed by Boehringer Ingelheim). Boehringer Ingelheim alleged that the claims were unsubstantiable, with respect to all of these points, were all-embracing and exaggerated the efficacy and safety of Olmetec in managing essential hypertension in breach of Clauses 7.2, 7.4 and 7.10 of the Code.

RESPONSE

Sankyo submitted that Boehringer Ingelheim had taken the phrase 'there's nothing better' out of context from the complete claim or consideration of the clear context in which it was being used.

Sankyo considered that it was important to explain the context and define the clarity of the advertisements with respect to the claims that were being made. Although the company understood and agreed that each case should be considered on its own merits it noted that previous cases where similar 'unbeaten' or 'unsurpassed' claims had been used, highlighted the need to consider the context of the supporting information with respect to such claims. In this regard Sankyo cited the rulings made in Cases AUTH/979/2/00, AUTH/980/2/00, AUTH/1021/5/00, AUTH/1108/11/00, AUTH/1149/2/01, AUTH/1272/1/02 and AUTH/1567/3/04.

Sankyo strongly contended that 'There's nothing better to get Yvonne bang on' and 'There's nothing better to get Margaret to target' were explicitly focused on the need for hypertensive patients to reach BP goals/targets. Sankyo did not consider that it could be interpreted in any other manner in the way that it was portrayed in each of the advertisements. This over-riding claim was further supported by the introductory text in each of the advertisements which provided the complete genre or 'feel' of the item in relation to hypertension and its treatment.

Sankyo noted that Boehringer Ingelheim had already interpreted the claims to be in the context of lowering blood pressure and managing essential hypertension. Sankyo did not consider therefore that the claim was misleading and the context was clear in terms of the

recognised patients being hypertensives. The introductory text further discussed the concept of achievement of a blood pressure reduction in mild-moderate hypertensives 'in light of the new GMS (General Medical Services) contract' ie to an inferred target, the GMS goal of 150/90mmHg which was now well recognised. Thus, the context of the advertisements (ie related to hypertension, efficacy in terms of blood pressure (BP) goal attainment, a specific patient population (mild-moderate hypertensives), and a well recognised and defined GMS goal (150/90mmHg)) was clear and the claims that 'There's nothing better to get Margaret to target' and 'There's nothing better to get Yvonne bang on', were thus not misleading, ambiguous or hanging comparisons.

Sankyo did not consider that the educated reader would interpret the claims to relate to anything wider than a product specific claim against other antihypertensives and did not consider that Boehringer Ingelheim's argument that the claim could relate to 'anything [pharmacological] or otherwise' ie implying non-pharmacological treatments, to be relevant. In a competitive environment it was highly unlikely that a pharmaceutical company would compare its treatment to non-pharmacological treatment in its advertisements in this particular patient population.

Sankyo noted that the advertisements then went on to introduce the results offered with Olmetec with respect to responder rates which were an important, but not the only, measure of response which helped quantify the proportion of patients achieving a diastolic BP goal of ≤ 90mmHg or a reduction in BP of ≥ 10mmHg. This figure was important in measuring response to treatment and goal/target attainment.

The prescriber was then offered a choice to use Olmetec to get a sense of achievement as part of their treatment in achieving BP targets.

Sankyo did not consider therefore that the claims were in breach of Clauses 7.2, 7.4 or 7.10 and did not consider them to be ambiguous, misleading or hanging comparisons as the context was clearly defined.

Sankyo noted that in previous cases the Panel had considered that 'unsurpassed' or 'unbeaten' meant that there was 'nothing better'. In this regard Sankyo considered that the claims 'There's nothing better to get Yvonne bang on' and 'There's nothing better to get Margaret to target' related to a claim of 'unbeaten efficacy' or 'unsurpassed performance' in hypertensive patients getting to a BP goal. The claims 'There's nothing better to get Yvonne bang on' and 'There's nothing better to get Margaret to target' established the position that there was nothing better than Olmetec but it did not discount that a product might be at least as good as Olmetec in terms of BP efficacy to get to target. This had been discussed on numerous occasions with similar claims.

Sankyo believed that the claims 'There's nothing better to get Yvonne bang on' and 'There's nothing better to get Margaret to target' reflected the fact that a review of the medical literature suggested that, currently, no licensed antihypertensive had surpassed Olmetec in head-to-head studies in terms of BP lowering efficacy, reaching defined BP goals, or demonstrating significantly higher responder rates. At best a comparator could claim that it was at least as good as Olmetec with respect to a single numerical BP measure but on balance the data suggested that the evidence was in favour of Olmetec and that there was no significant superiority demonstrated by any other antihypertensive tested.

Furthermore Sankyo understood from previous cases that when 'top parity' claims of this type were made it was considered that at the very minimum, evidence from controlled head-to-head studies showing no difference should be used. Olmetec had easily achieved this minimum standard as where it had been compared against the majority of other groups of antihypertensive in head-to-head studies, it had demonstrated in most cases at least significantly better lowering of blood pressure. This evidence therefore substantiated the claims made.

Olmetec had been compared in head-to-head studies against AIIAs, ACE inhibitors, beta-blockers and calcium channel blockers with different features of BP efficacy being measured. In total these studies had included the following key BP efficacy measurements: responder rates, normalisation rates, ambulatory blood pressure monitoring goal rate attainment, cuff goal rate attainment, diastolic BP reduction, systolic BP reduction, 24 hour control and BP control in the early hours. A tabulated summary of the data was provided.

Furthermore, in relation to Boehringer Ingelheim's complaint with respect to the consideration of its product Micardis, Sankyo requested that it provided efficacy data to demonstrate superiority over Olmetec. Sankyo was not aware of such data and no such data had been provided to support Boehringer Ingelheim's complaint. Furthermore Sankyo noted that Micardis had been shown to be inferior to other antihypertensives to which Olmetec had demonstrated superiority (Calvo *et al* 2004). The claims therefore that 'There's nothing better to get Margaret to target' or 'to get Yvonne bang-on' stood and were thus not unsubstantiated, all embracing or exaggerated with respect to Clauses 7.2, 7.4 or 7.10.

Sankyo further considered that there was strong supporting evidence from several past cases that the claim 'There's nothing better …' was supported by precedent and was not therefore misleading, exaggerated or all-embracing. Furthermore Sankyo considered the wealth of evidence which existed substantiated the claims and that there was no licensed antihypertensive, available in the UK, to Sankyo's knowledge which demonstrated superiority over Olmetec.

Further reinforcement with regard to reaching target was to be found in two studies.

In a recently completed observational study (OLMEPAS – data on file) approximately 12,000 patients in Germany received olmesartan as monotherapy for the treatment of hypertension and were followed over a 12 week period. At the second follow-up visit 80.9% of patients were shown to be 'responders' defined as a reduction of diastolic BP to

< 90mmHg and/or improvement of diastolic BP ≥10mmHg compared to baseline and 64.3% of the patients were 'normalised' (a reduction of diastolic BP<90mmHg).

In a second phase IIIb study (OLMEBEST – data on file), approximately 3000 patients in 10 centres across Europe received olmesartan for the treatment of essential hypertension. The open treatment phase analysis was now complete and an additional analysis for UK patients was performed over an 8 week period. The results showed that following the second follow-up visit an average of 73% of patients were shown to be 'responders' whilst 64% of patients were 'normalised' (defined as above).

These data on file surpassed the data presented by Puchler (2001).

In summary Sankyo considered that each case had to be judged on its own merits but equally respected that case precedents helped ensure that high levels were maintained with respect to the Code. In this regard Sankyo firmly considered that the claims used were not in breach of Clauses 7.2, 7.4 or 7.10 and fulfilled all the criteria required to ensure that they were substantiated, were not all-embracing, were not exaggerated, did not mislead or create ambiguity and did not include hanging comparisons.

Sankyo therefore considered that Boehringer Ingelheim's complaint was not supported by precedent, and the evidence Sankyo had provided demonstrated that these claims were supported by evidence. Sankyo did not believe that it was in breach of the Code.

PANEL RULING

The Panel did not consider that the claims 'There's nothing better to get Yvonne bang on' or 'There's nothing better to get Margaret to target' were hanging comparisons as alleged. The Panel considered that in the context in which the claims appeared it was clear that the comparison was with all other antihypertensives. The Panel ruled no breach of Clause 7.2 in that regard.

The Panel considered that the claims at issue suggested that whilst other antihypertensive therapies/regimens might match Olmetec, in terms of getting patients to BP targets, none could better it. Sankyo had cited past cases in support of its position. The Panel considered, however, that every case had to be considered on its own merits. The context in which a claim appeared was important.

The Panel considered that the claims at issue implied that no other antihypertensive therapy/regimen was better than Olmetec at reducing patients' blood pressure to target. The claims did not exclude the possibility that another antihypertensive therapy/regimen might be equally efficacious. The Panel noted that Sankyo had referred to a number of studies to support the claims. These studies, however, did not include head-to-head trials of Olmetec versus every other antihypertensive therapy/regimen. The data supplied by Sankyo showed that Olmetec monotherapy had only been compared with monotherapy with three AIIAs (losartan, valsartan and irbesartan), one beta-blocker (atenolol), one ACE inhibitor (captopril) and one calcium channel blocker (felodopine). No data was provided comparing Olmetec with combination therapy. The Panel considered that the claims 'There's nothing better ...' were broad unequivocal claims which suggested that every other antihypertensive therapy/regimen had been compared with Olmetec and that none had been shown to be more efficacious. This was not so. The Panel considered in that regard that the claims were misleading, exaggerated and thus could not be substantiated. Breaches of Clauses 7.2, 7.4 and 7.10 were ruled.

Complaint received **24 February 2005**

Case completed **3 May 2005**

CASES AUTH/1682/2/05 and AUTH/1683/2/05

GENERAL PRACTITIONER and MEDIA/DIRECTOR v ASTRAZENECA

Arrangements for meetings

In Case AUTH/1682/2/05 a general practitioner complained about a residential meeting for nurses to be held by AstraZeneca at a hotel on Loch Lomond. According to the invitation/agenda the meeting started on a Friday evening at 7.15pm and finished at 11.15am the next day. The complainant alleged that the hospitality offered was excessive for roughly three hours of education.

Case AUTH/1683/2/05 concerned an article in The Sunday Times entitled 'Drugs giants court NHS nurses with luxury hotel breaks' which noted that AstraZeneca had entertained nurses and doctors at a four star hotel in Glasgow, providing a 45 minute presentation before treating its guests to dinner. The article also noted that 50 nurses had been invited to a hotel in Lincolnshire and reference was made to the meeting arranged on Loch Lomond.

With regard to the meeting on Loch Lomond (Cases AUTH/1682/2/05 and AUTH/1683/2/05), the Panel noted that it had been cancelled. The Code, however, referred to the offer of hospitality and so invitations were covered even if the meeting was not held. The Panel thus made its rulings on the basis of the meeting as described in the invitation.

The Panel noted that the meeting was aimed at nurses who specialised in the treatment of asthma and COPD in the community. According to the agenda the meeting was to start on a Friday evening at 7.15pm and finish that day with dinner at 9pm. The following day's session started at 9.30am and finished at 11.15am. The Panel noted AstraZeneca's submission that a further 90 minute training session was to have been added to the second day. This was not, however, the basis on which the invitation was issued.

The Panel questioned whether, even with the additional session, the hospitality would have been secondary to the main purpose of the meeting. Five hours of education could be held on one day without the need for overnight accommodation. The title of the meeting 'Well Maintained @ Loch Lomond' compounded the impression of substantial hospitality. The Panel queried whether the expected cost per head (£185) was what delegates would have paid for themselves. The arrangements were unacceptable, high standards had not been maintained. Breaches of the Code were ruled including a ruling of a breach of Clause 2.

AstraZeneca accepted that it had not maintained high standards but appealed the other rulings of a breach of the Code. The Appeal Board considered that the limited educational content described on the invitation as issued meant that the hospitality offered was not secondary to the main purpose of the meeting. Delegates would be attracted by the prestigious spa venue and not the educational content. The title of the meeting 'Well Maintained @ Loch Lomond' compounded the impression of substantial hospitality and the graphics on the invitation accentuated the feeling of a spa venue. The Appeal Board considered that the invitation as issued was totally unacceptable and upheld the Panel's rulings of breaches of the Code including the ruling of a breach of Clause 2.

With regard to the meeting at the hotel in Glasgow (Case AUTH/1683/2/05) the Panel noted that the invitation showed that it would begin at 7.15pm and at 7.30pm there would be a presentation on asthma/COPD. Discussion and questions would follow at 8.15pm and dinner would be served at 8.30pm. The agenda for the actual meeting was different in that after the first speaker an additional 45 minute presentation was added and dinner was served at 9pm. The updated agenda was given to the nurses as they arrived at the meeting. A two course set meal was served in a private room at a cost of £27.80/head including drinks.

The Panel noted AstraZeneca's submission that it was common practice to add details to an agenda after invitations had been sent. The Panel considered, however, that the addition of a 45 minute presentation went beyond the fine tuning referred to by AstraZeneca. The arrangements for the meeting as described on the invitation were unacceptable. The educational content was not sufficient to justify the hospitality. High standards had not been maintained. Breaches of the Code were ruled. With regard to the actual meeting the Panel considered that it was not inappropriate; the balance between hospitality (£27.80/head) and the education ($1^1/_2$ hours) was on the limits of acceptability, no breach of the Code was thus ruled.

The Panel noted that the meeting in Lincolnshire (Case AUTH/1683/2/05) was an all day meeting of a regional asthma forum sponsored by AstraZeneca. For each of the 70 delegates, GPs, nurses and pharmacists, AstraZeneca paid £50 for the day plus £109 bed and breakfast for the 10 committee members. The Panel considered that the hospitality was secondary to the main purpose of the meeting. The meeting had a clear educational content that was relevant to the audience. No breach of the Code was ruled.

Case AUTH/1682/2/05

Meeting arranged at Loch Lomond

A general practitioner in Glasgow complained about an invitation to a meeting for nurses to be held by AstraZeneca UK Limited on Friday/Saturday, 18-19 February, at an hotel on Loch Lomond. A copy of the invitation/agenda was provided. The meeting was entitled 'Well Maintained @ Loch Lomond' and, according to the agenda, commenced on the Friday at 7.15pm with registration; the formal part of the evening started at 7.30pm and closed at 9pm. On the Saturday morning a presentation commenced at 9.30am and closed with questions and discussion at 11.15am.

COMPLAINT

The complainant alleged that the meeting breached the Code; the hospitality was excessive for roughly three hours of education and was the primary inducement for attendance.

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

RESPONSE

AstraZeneca stated that the meeting was initially organised by its representatives based in the West of Scotland region to provide local nurses who specialised in the treatment of asthma and chronic obstructive airways disease (COPD) in the community with an educational update meeting on these disease. The invited speakers were well known local experts in the therapy area.

The venue on Loch Lomond was chosen because the 24-hour delegate rate of £185 included all costs for an overnight stay, meeting facilities, refreshments and meals. AstraZeneca noted that the bed and breakfast rate for the hotel for the same weekend was £60 per person per night. The hospitality costs associated with the meeting were therefore no more than attendees would be expected to pay for themselves. AstraZeneca also noted that the hotel was conveniently located for all delegates invited who were based within the wide geographic location of the West of Scotland as they had to arrive by 7pm on a Friday evening. It was also reasonably near to Glasgow airport for one of the key speakers who was to arrive that evening from Belfast. The weekend time period was chosen after discussion with a number of the nurses who were to be invited. A meeting for Friday evening and part-day Saturday was the preferred option to enable them to attend because of travel distances and to make efficient use of their weekend.

The meeting was cancelled on 4 February following an internal review which indicated that the agenda required revision. All invitees to the meeting were therefore informed two weeks before the scheduled date that the meeting had been cancelled. As the meeting was cancelled AstraZeneca did not have any invoices but provided the quoted costs. The event contract form for the meeting provided details of timings relating to the agenda.

AstraZeneca stated that the sales team arranging the agenda had originally planned to incorporate a further 90-minute training session from an AstraZeneca nurse specialist to take place on Saturday, 19 February, from 11.30 to 1pm. This additional session as well as lunch was not included in the original agenda mailed to invitees; on reflection the team acknowledged this as an error. The contract with the hotel clearly showed that the meeting was planned to run to lunchtime on 19 February.

AstraZeneca had a strict process to ensure that meetings and associated hospitality complied with the Code and internal corporate governance policies. Following the 27 February article entitled 'Drug giants court NHS nurses with luxury hotel breaks' in The Sunday Times [see Case AUTH/1683/2/05 below] the whole UK marketing company including the entire salesforce was briefed and reminded of AstraZeneca's guidance on good meeting policy.

There was no intention to mislead the audience with the meeting agenda that was sent out. The meeting did not take place and there had been appropriate follow-up action in terms of re-briefing the entire company on AstraZeneca Meetings Guidelines. AstraZeneca therefore denied that this meeting was in breach of Clauses 2, 9.1 and 19.1 of the Code.

PANEL RULING

The Panel noted that Clause 19.1 of the Code permitted companies to provide appropriate hospitality to members of the health professions and appropriate administrative staff in association with scientific and promotional meetings. Hospitality must be secondary to the purpose of the meeting and the level of hospitality offered must be appropriate and not out of proportion to the occasion. The costs incurred must not exceed the level which recipients would normally adopt if paying for themselves. It must not extend beyond members of the health professions or appropriate administrative staff. The supplementary information stated that the impression created by the arrangements must be borne in mind.

The Panel noted that the complaint concerned the invitation. The meeting had been cancelled. The Code referred to the offer of hospitality at meetings. Invitations to meetings were covered even if the meetings were not held.

The Panel noted that the meeting was aimed at local nurses who specialised in the treatment of asthma and COPD in the community. According to the agenda it was to commence on Friday evening at 7.15 with registration, followed by a welcome, introduction and session entitled 'COPD: Back to basics' and to finish for that day with dinner at 9pm. The printed agenda showed that the educational content the next day (Saturday) was due to start at 9.30am and finish at 11.15am. The Panel noted AstraZeneca's submission that an AstraZeneca nurse specialist was to provide a further 90 minute training session which meant that in reality the meeting would have finished with lunch at 1pm. This however was not the basis on which the invitation was issued.

The Panel questioned whether, even with the additional 90 minutes of education not referred to on the printed agenda, the hospitality would have been secondary to the main purpose of the meeting. Although the invited delegates were from a large geographical area the meeting which was to have less than five hours of education (including the additional session) plus registration time could have been held over one day without the need to provide overnight accommodation. Delegates would be attracted by the venue and the associated hospitality and not by the educational content. The title of the meeting 'Well Maintained @ Loch Lomond' compounded the impression of substantial hospitality given by the invitation. The Panel noted that although the delegates' preferred option was to hold the meeting on Friday night and over into Saturday, AstraZeneca's

first priority was to ensure that the meeting arrangements complied with the Code regardless of its customer's wishes.

The Panel queried whether the expected cost of the hospitality at £185 per head was in line with what invitees would pay if they were paying for themselves.

The arrangements were unacceptable. AstraZeneca had offered an overnight stay at a prestigious hotel in association with just over 3 hours of education. The Panel ruled a breach of Clause 19.1. This ruling was appealed. The Panel considered that high standards had not been maintained and therefore ruled a breach of Clause 9.1 of the Code. This ruling was not appealed.

The Panel noted that Clause 2 of the Code stated that activities or material associated with promotion must never be such as to bring discredit upon or reduce confidence in the pharmaceutical industry. A ruling of a breach of Clause 2 was a sign of particular censure and was reserved for such circumstances. The Panel considered that the meeting as described by the invitation was such as to warrant a ruling of a breach of this clause and ruled accordingly. This ruling was appealed.

Case AUTH/1683/2/05

An article entitled 'Drug giants court NHS nurses with luxury hotel breaks' which appeared in The Sunday Times on 27 February 2005 criticised the activities of, *inter alia*, AstraZeneca UK Limited. In accordance with established practice the matter was taken up by the Director as a complaint under the Code of Practice.

COMPLAINT

The Sunday Times article referred to a number of meetings including the one planned at Loch Lomond (the subject of Case AUTH/1682/2/05 above).

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

RESPONSE

AstraZeneca stated that it was particularly concerned about the article and disappointed that the journalist had misrepresented some of the facts regarding the meeting. The article contained factual inaccuracies and full details of the respective agendas were not given. AstraZeneca denied breaches of Clauses 2, 9.1 and 19.1.

AstraZeneca advised that with regard to the meeting to be held at Loch Lomond its response in Case AUTH/1682/2/05 applied here (see above).

PANEL RULING

With regard to the points raised in The Sunday Times article, the Panel noted that the Code and UK law allowed medicines to be promoted to health professionals and this would include nurses. Such activity had to comply with the Code.

The Panel considered that in relation to the meeting to be held at Loch Lomond its rulings in Case AUTH/1682/2/05 of breaches of Clauses 2, 9.1 and 19.1 applied (see above).

Cases AUTH/1682/2/05 and AUTH/1683/2/05

APPEAL BY ASTRAZENECA

AstraZeneca explained that the meeting was organised by its representatives in the West of Scotland region and was aimed at local nurses who specialised in the treatment of asthma and COPD in the community. The objective of the meeting was to provide an AstraZeneca sponsored educational meeting on disease areas relevant to practice nurses that managed respiratory conditions in the community. The invited speakers were selected on the basis of their expertise in managing asthma and COPD as well as being well known to the local respiratory medical community.

1 Costs

AstraZeneca submitted that the quoted 24-hour delegate rate given by the hotel at the time of enquiry was £185 per delegate which included all associated costs for a one night stay ie bed and breakfast (£112), lunch (£18), dinner (£25); meeting facilities, room hire, refreshments and coffee made up the balance of the 24 hour delegate rate.

AstraZeneca submitted that the bed and breakfast rate represented good overall value for this type of meeting and was reasonable. In addition £18 for a buffet lunch and £25 for dinner was a reasonable sum and was no more than what attendees would be expected to pay for themselves. In addition customers would not normally pay for refreshments and room hire costs themselves.

AstraZeneca referred to the Panel's ruling in Case AUTH/1683/2/05 concerning the LEAF meeting that was held at the Belton Woods Hotel (see below). This meeting included practice nurses amongst the attendees. The Panel had not considered that £109 for overnight accommodation and breakfast to be more than attendees would be expected to pay for themselves.

2 Travel logistics

AstraZeneca submitted that the hotel had to be conveniently located for all delegates invited who were based within the wide geographic location of the West of Scotland, as they had to arrive by 7pm on a Friday evening. It also had to be reasonably near Glasgow airport for one of the key speakers who was to arrive that evening from Belfast. The weekend was chosen after discussion with a number of the nurses who were to be invited. A meeting for Friday evening and part-day Saturday was the preferred option to enable them to attend because of travel distances and to make efficient use of their weekend time. A one-day meeting would have been unreasonable given that some of them would have had to drive for up to two to three hours to the venue. Many invitees would have to travel along minor

roads that were ubiquitous in the West coast region of Scotland.

AstraZeneca acknowledged the Panel's comment that although the delegates' preferred option was to hold the meeting on Friday night and over into Saturday, it was AstraZeneca's first priority to ensure that the meeting arrangements complied with the Code regardless of its customers' wishes. AstraZeneca maintained that it was reasonable to hold an educational meeting with this schedule to take into account travel logistics, minimising the delegates' time away from their practice, and making efficient use of weekend time. This demonstrated respect for health professionals' time, which had not appeared to be taken into account in this complaint.

AstraZeneca submitted that the total educational content of the meeting with well regarded speakers was to be $1^1/_2$ hours on the Friday evening and $3^1/_4$ hours on the Saturday which included the planned additional 90 minute training session closing at 12.45pm for lunch. An overnight stay was therefore required, as the five hours of educational content could not have been completed in one full day given the travelling times and logistics for many of the invitees.

On the basis of points 1 and 2 above, AstraZeneca submitted that the arrangements for the meeting were not in breach of Clause 19.1 of the Code.

3 Impression created by the invitation

AstraZeneca submitted that the title of the meeting 'Well maintained @ Loch Lomond' was not intended to create the impression that delegates would receive overly generous hospitality but was used as a well-intentioned pun relating to maintenance strategies for asthma and COPD treatment which were the focus of the meeting. The audience fully understood the use of the words in the meeting title but AstraZeneca acknowledged that different wording would have been more appropriate.

4 AstraZeneca's prompt action

AstraZeneca submitted that it became aware of concerns regarding the meeting when a journalist contacted the press office. AstraZeneca then conducted an internal review and took prompt action regarding the meeting as initial scrutiny of the invitation indicated that the agenda required revision. On the 4 February it cancelled the meeting, and all invitees to the meeting were therefore informed two weeks before the scheduled date. This cancellation occurred over three weeks before the publication of The Sunday Times article on 27 February 2005.

AstraZeneca submitted that it took any complaints regarding its meetings very seriously; it had a strict process to ensure that meetings and associated hospitality fully complied with the Code and internal corporate governance policies. A full investigation was ongoing with the sales staff concerned with this meeting and appropriate action would be taken. Following The Sunday Times article entitled 'Drug giants court NHS nurses with luxury hotel breaks' the whole UK marketing company including the entire sales force were briefed and reminded of AstraZeneca's guidance on good meeting policy. In addition, AstraZeneca had instigated a full review of planned external meetings to ensure compliance with the Code and was in the process of making further reinforcements to the meeting policy.

AstraZeneca acknowledged that in making its rulings the Panel considered the meeting invitation, which had not contained full details of the planned meeting. Therefore AstraZeneca took the decisive action to ensure that it did not bring the industry into disrepute by cancelling the meeting and also briefing the organisation on meetings' policy; the Clause 2 ruling was thus not warranted. AstraZeneca drew parallels between this case and a similar case regarding meeting arrangements, Case AUTH/1534/10/03, in which the Panel did not consider that the arrangements warranted a ruling of a breach of Clause 2. AstraZeneca considered that it had not brought the industry into disrepute and therefore appealed the Panel's ruling of a breach of Clause 2.

Case AUTH/1682/2/05

COMMENTS FROM COMPLAINANT

The complainant alleged that irrespective of the initial quotation the delegate cost to AstraZeneca was £185. This did not include expenditure on alcohol. In the complainant's view a bottle of wine would cost in the order of £20 so the true cost would have been over £200. The average hourly rate of a practice nurse was £15 therefore allowing for taxation, £200 spent on this one night would represent 20 hours' work, or roughly one week's wages for a part time nurse. How many working people would spend a week's wages on a night of 'education'? This must be deemed disproportionate and an inducement to attend.

The complainant noted that health professionals were public servants many of whom worked in deprived areas. The current weekly state pension for a single person was £67, therefore the money spent on this one night 'education' per delegate represented almost one month's worth of pension. Public opinion dictated probity therefore AstraZeneca and the Appeal Board must accept how inappropriate this all seemed to patients.

The complainant noted that AstraZeneca maintained that the weekend was chosen following consultation with nurses. If the nurses had suggested a foreign destination would the company have similarly bowed to these requests?

The complainant disputed AstraZeneca's suggestion that the venue was chosen for its 'convenient' geographical location. Glasgow would have been the obvious hub for this meeting with its extensive communication infrastructure. The complainant enquired how many delegates were due to attend from outlying areas, and suggested that most delegates were in fact from Glasgow and indeed would need to travel for 40-60 minutes to reach the meeting. The venue was chosen because of its reputation for hosting celebrities, extensive leisure facilities and the idea that this could be presented as 'a weekend away'.

The complainant noted that 90 minutes of additional education had appeared on the programme and this had been described as an 'error'. The complainant questioned if in fact this was an attempt to cover tracks, as this seemed a major oversight. The complainant referred to another meeting run by AstraZeneca [Case AUTH/1688/3/05] where additional education miraculously appeared due to a similar 'error' on the invitation.

The complainant noted that the meeting was cancelled in haste. If there was not an issue with the level of hospitality why should the company cancel the meeting at all? It seemed obvious that this event was cancelled due to the publicity and as an attempt to limit the damage.

The phrase on the invitation 'Well maintained' could indeed relate to asthma/COPD but seemed much more likely to be suggestive of the hospitality on offer.

The complainant noted that the company cited a ruling in Case AUTH/1534/10/03. The complainant stated that he had been a full time GP for 10 years and knew the system. Everybody had mutual interests in keeping quiet. This meeting, like so many others, was centered around hospitality with some token education. Once rumbled the company sought to explain, excuse and misdirect but the facts spoke for themselves. This was an industry wide problem with a corporate responsibility and not merely a case of rogue sales staff as claimed in previous rulings. Rather than the rulings in Case AUTH/1534/10/03 mitigating AstraZeneca's ruling of a breach of Clause 2, the Appeal Board should review the ruling in that case.

The complainant noted that he was involved with a group called 'nofreelunch', which was not anti industry but merely against excessive marketing and irresponsible hospitality. The ABPI was currently charged with the public duty to regulate this multi billion pound industry but the environment was changing. What was acceptable a few years ago was no longer.

The complainant quoted Sir Richard Sykes, 'Today the industry has got a very bad name. That is very unfortunate for an industry that we should look up to and believe in, and that we should be supporting. I think there have to be some big changes'.

The complainant alleged that AstraZeneca had cynically breached the Code and should be reprimanded accordingly.

Case AUTH/1683/2/05

Comments from The Sunday Times

The Sunday Times provided no comments.

Cases AUTH/1682/2/05 and AUTH/1683/2/05

Appeal Board Ruling

The Appeal Board noted that AstraZeneca's reasons for appeal appeared to be based on what should have happened at the planned meeting and the fact that it cancelled the meeting once it saw the invitation. The Appeal Board considered, however, that its role was to rule on what had happened.

The Appeal Board noted that the AstraZeneca representatives stated at the appeal hearing that, in accordance with the company's meetings guidelines, meetings which included an overnight stay had to be approved by head office. Whilst the scope of the meeting had been approved and the artwork was pre-approved, the overall arrangements had not been approved in accordance with AstraZeneca's meetings guidelines. The Appeal Board was extremely concerned that this failure to comply with company procedures was only revealed at the appeal hearing and was not referred to in any of the foregoing correspondence. The AstraZeneca representatives could not explain this omission other than to state that the investigation was ongoing and their presentation reflected the current position.

Similarly, at the appeal hearing it was noted for the first time that the extra 90 minute training session related to discussion of the Zoladex Safe System, the Chairman's opening remarks and best practice sharing and the Chairman's closing remarks. These details had not been provided in the correspondence.

The Appeal Board was concerned that the invitation included a section for the recipient to complete plus an opportunity for the recipient to include colleagues. The Appeal Board considered that there was a possibility that 'colleagues' could include those who were not health professionals. In mitigation the AstraZeneca representatives stated that the invitations were used following a verbal discussion with the representatives.

The Appeal Board considered that the limited educational content described on the invitation as issued meant that the hospitality offered was not secondary to the main purpose of the meeting. The meeting as described on the invitation with just over 3 hours of education could have been held over one day without the need to provide overnight accommodation. The Appeal Board noted that the west of Scotland was a large area and travel was difficult, however, it queried whether the venue was a truly convenient location for the majority of delegates. The Appeal Board noted the prestigious, spa reputation of the hotel and considered that delegates would be attracted by the venue and the associated hospitality and not by the educational content. The title of the meeting 'Well Maintained @ Loch Lomond' compounded the impression of substantial hospitality and the graphics on the invitation accentuated the feeling of a spa venue.

The Appeal Board noted AstraZeneca's submission regarding the expected cost of the hospitality. The Appeal Board queried whether the per head cost (£185 if room hire was included or £155 without room hire) was in line with what nurses would pay for themselves. The costs did not appear to include drinks with lunch or dinner.

The Appeal Board considered that the invitation as issued was totally unacceptable and upheld the Panel's ruling of a breach of Clause 19.1. The appeal on this point was unsuccessful.

The Appeal Board noted that a ruling of a breach of Clause 2 was a sign of particular censure and was reserved for such circumstances. The Appeal Board

considered that the meeting as described in the invitation was such as to warrant a ruling of a breach of this clause and upheld the Panel's ruling. The appeal on this point was unsuccessful.

Case AUTH/1683/2/05

Meetings arranged in Glasgow and Lincolnshire

COMPLAINT

The Sunday Times article stated that the previous week AstraZeneca had entertained nurses and doctors at a four-star hotel in Glasgow. The company, which made asthma products, provided a 45 minute presentation before treating its guests to dinner. The restaurant menu offered pan-fried woodpigeon breast with orange and shaved beetroot followed by roast Gressingham duck breast and blueberry and praline feuillete. Similar invitations were being extended across the country.

The article also stated that in 2004 about fifty nurses had been invited by AstraZeneca to a four-star hotel in Lincolnshire to discuss asthma.

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

The meeting at the Glasgow hotel was also the subject of a separate complaint: Case AUTH/1688/3/05.

RESPONSE

AstraZeneca stated that it was particularly concerned about the article and disappointed that the journalist had misrepresented some of the facts regarding the meetings. The article contained factual inaccuracies and full details of the respective agendas were not given. AstraZeneca denied breaches of Clauses 2, 9.1 and 19.1.

1 Meeting in Glasgow

The title of this meeting was 'Asthma/COPD and the GMS contract' and was set up as an educational evening meeting for practice nurses who specialised in running asthma and COPD clinics. The agenda was focused on the new GMS contract within primary care relating to management of COPD and asthma. The GMS contract relating to respiratory disease was a topical area for asthma specialised practice nurses. The invitees were chosen by the local sales team based on their specific interest in COPD and asthma.

The main speaker was to provide a 45 minute educational presentation on details of the GMS contract relating to managing chronic respiratory disorders, COPD and asthma within primary care. A further speaker, a practice nurse, was later added to the agenda following her confirmation after the initial preliminary invitation had been sent out. She was to provide further information on how the GMS contract related specifically to the asthma clinic nurse and discuss particular case studies. The updated agenda was distributed to the 17 attending asthma nurses on arrival.

It was common meeting practice that further details on exact timings and speakers' names and titles were added to an agenda after an invitation had been sent out. This was to provide sufficient time for invitees to consider their attendance as well as time to allow speakers to confirm their attendance.

The total presentation and discussion period lasted two hours which was considered appropriate in terms of educational content for an evening meeting. The meeting was followed by a two course set dinner. The meeting and the dinner were held in a private room. The menu consisted of a choice of either tuna or chicken for the main course and a choice of two desserts; it was not the pan-fried woodpigeon breast and roast Gressingham duck as alleged in The Sunday Times. The dinner cost per head was £19 for the two courses. The total bill including drinks for the 15 attendees who ate was £417. This equated to £27.80 per head for a two-course meal and drinks which represented good value for the meal served and was no more than attendees would be expected to pay themselves.

2 Meeting in Lincolnshire

A meeting of a regional asthma forum at a hotel in Lincolnshire held on Friday, 19 November 2004, was made possible by an unrestricted educational grant from AstraZeneca. The format of the meeting and selection of speakers and topics was determined by the forum committee. There were no AstraZeneca promotional stands or activities at the meeting.

The invitation for the meeting was sent directly by the forum committee and replies were sent to an associate director in general practice. The meeting agenda was purely educational in nature and highly clinically relevant and was determined by members of the forum committee and not by AstraZeneca. The invitation clearly reflected the educational basis of the meeting and the forum initiative.

Seventy GPs, practice nurses, hospital respiratory nurses and pharmacists attended the meeting. It was entirely appropriate to have a multidisciplinary audience for such a meeting. None of the meeting delegates stayed overnight, only the forum committee and one of the speakers arrived the night before, Thursday, 18 November, for a preparatory two hours briefing meeting.

AstraZeneca was the sole sponsor of the meeting. The costs associated with this sponsorship included a £50 per person day delegate rate as well as a £109 per person bed and breakfast for each of the ten committee members who had arrived the evening before. The total invoice for the meeting was £4,940 for the 70 delegates. The drinks bill only came to approximately £220 and included drinks for the 10 delegates staying overnight and the cost of soft drinks for all 70 delegates at lunch the following day. AstraZeneca did not pay for any travel costs associated with this meeting.

AstraZeneca submitted that the arrangements made by the forum committee were in line with the Code's requirements regarding companies providing hospitality for health professionals. The chosen hotel was a suitable venue with excellent audiovisual meeting facilities for such an educational meeting.

None of the costs incurred by the independent forum committee were above what would be expected for delegates to pay themselves. The meeting was held in a private room. Dining was in the hotel's main restaurant at pre-booked tables away from the hotel's other guests.

AstraZeneca therefore denied that these two meetings were in breach of Clauses 2, 9.1 and 19.1 of the Code.

PANEL RULING

As in its consideration of Case AUTH/1682/2/05 above, the Panel noted the requirements of Clause 19.1 of the Code. The supplementary information stated that the impression created by the arrangements must be borne in mind.

With regard to the points raised in The Sunday Times article, the Panel noted that the Code and UK law allowed medicines to be promoted to health professionals and this would include nurses. Such activity had to comply with the Code.

1 Meeting in Glasgow

The Panel noted AstraZeneca's submission that the meeting in question was for asthma/COPD nurses. The letter of invitation provided by the complainant, however, began 'Dear Doctor' to which someone had added, in handwriting '/Nurse'. The letter had been signed by an AstraZeneca representative and it appeared that she had added to the bottom of the letter 'Give me a call and let me know if you can make it. Also any GPs that want to attend. Thanks'. It further appeared that the complainant, a GP, had not attended the meeting; the complaint had been made on the basis of the invitation sent by AstraZeneca. The invitation stated that the meeting would begin at 7.15pm and at 7.30pm the speaker would deliver a presentation entitled 'Asthma/COPD and the GMS Contract'. Discussion and questions would follow at 8.15pm and dinner would be served at 8.30pm. There was no mention that a second speaker would be present thus extending the educational content of the meeting until 9pm.

The agenda for the actual meeting was different in that after the first speaker an additional 45 minute presentation by a practice nurse was added and dinner was to be at 9pm. The additional presentation provided further information on how the GMS contract related specifically to the asthma clinic nurse and particular case studies. The updated agenda was given to 17 asthma nurses when they arrived for the meeting.

The Panel noted that The Sunday Times article referred to the menu in the restaurant. This was not available to the delegates at the meeting. A two course set meal was served in a private room and cost £27.80 per head including drinks.

The Panel noted that from the original agenda the planned educational content was an hour followed by dinner in a private room. The agenda for the actual meeting had been extended by 30 minutes. It was not known what time the meeting finished. The bill gave the time as 10.22pm.

The Panel noted AstraZeneca's submission that it was common practice that further details on exact timings and speakers' names and titles were added to an agenda after an invitation had been sent out. The Panel noted, however, that the supplementary information to Clause 19.1 stated that with any meeting, it should be the programme that attracted delegates and not the associated hospitality or venue. AstraZeneca had issued invitations to a meeting which had shown that there would only be one hour of educational content; the full programme had not been disclosed in the agenda and so it was thus possible that some attendees at least had accepted the invitation on the basis of the hospitality offered. The Panel considered that although details of meeting agendas could be changed nearer the time the addition of a 45 minute presentation went beyond fine tuning timings or adding speakers' names and titles as submitted by AstraZeneca.

The arrangements for the meeting as described on the invitation were unacceptable. The educational content was not sufficient to justify the hospitality. A breach of Clause 19.1 was ruled. The Panel considered that in relation to the invitation high standards had not been maintained and ruled a breach of Clause 9.1.

The Panel noted that Clause 2 of the Code stated that, *inter alia*, activities associated with promotion must never be such as to bring discredit upon, or reduce confidence in, the pharmaceutical industry. A ruling of a breach of Clause 2 was a sign of particular censure and was reserved for such circumstances. The Panel did not consider that the invitation was such as to warrant a ruling of breach of this clause and so no breach of Clause 2 was ruled.

The Panel considered that the published criticisms of the arrangements went beyond the invitation and concerned the meeting itself. Taking all the circumstances into account the Panel considered that the actual meeting in Glasgow was not inappropriate. In the Panel's view the cost of dinner (£27.80/head) was on the limits of acceptability in terms of what the delegates might expect to pay if paying for themselves. Similarly the balance between hospitality and education was on the limits of acceptability. Nonetheless the meeting had a clear educational content that was relevant to the audience. On balance, the hospitality was not unreasonable and was secondary to the main purpose. The Panel therefore ruled no breach of Clause 19.1 of the Code.

2 Meeting in Lincolnshire

The Panel noted that the meeting was an all day meeting (9.30am (registration) – 4.30pm) of a regional asthma forum. AstraZeneca had sponsored the meeting.

The 70 delegates were a mixture of GPs, practice nurses, hospital respiratory nurses and pharmacists. The costs paid by AstraZeneca were £50 per person per day plus £109 bed and breakfast for the 10 forum committee members. There had been a briefing meeting the night before which one of the speakers had attended. No travel costs were paid.

The Panel considered that the hospitality was secondary to the main purpose of the meeting. The level was appropriate and not out of proportion to the occasion. The cost of £50 for a day delegate plus £109 for the overnight accommodation and breakfast for the ten committee members was within the level recipients would normally pay if they were paying for themselves. The meeting had a clear educational content that was relevant to the audience. The hospitality was secondary to the main purpose. The Panel therefore ruled no breach of Clause 19.1 of the Code.

The Panel did not consider that the arrangements failed to maintain high standards and no breach of Clause 9.1 was ruled. The arrangements were also ruled not to breach Clause 2 of the Code.

Case AUTH/1682/2/05
Complaint received **24 February 2005**

Case completed **13 June 2005**

Case AUTH/1683/2/05
Proceedings commenced **28 February 2005**

Case completed **13 June 2005**

CASE AUTH/1684/2/05 *NO BREACH OF THE CODE*

MEDIA/DIRECTOR v GLAXOSMITHKLINE

Hospitality at meeting

An article entitled 'Drug giants court NHS nurses with luxury hotel breaks' in The Sunday Times criticised the activities of, *inter alia*, GlaxoSmithKline and stated that it had held a dinner for nurses at a four-star hotel to discuss diabetes treatment, a condition in which it had a commercial interest. In accordance with established practice the matter was taken up by the Director as a complaint under the Code.

The Panel noted that the meeting started at 7.30pm with a buffet dinner. The speaker, presented for approximately an hour on a target based approach to primary care diabetes management. The audience was nurse specialists and a few general practitioners. The cost of the buffet was £15.25 although the actual per head cost was £27.37 due to the difference between the numbers expected (70) and those actually attending (39). No travel expenses were paid and attendees departed shortly after the close at 9pm.

The Panel considered that the hospitality was secondary to the main purpose of the meeting. The level was appropriate and not out of proportion to the occasion. Half an hour was allowed for registration and the buffet before the presentation started. The cost of £27.37 per delegate was not unreasonable although the Panel considered that it was on the limits of the level that the recipients would normally pay if they were paying for themselves. The presentation would be relevant to specialist nurses in primary care although its length, one hour plus questions, was on the limits of acceptability.

Taking all the circumstances into account the Panel considered that on balance the meeting was acceptable. It had a clear educational content that was relevant to the audience. The hospitality, which lasted 30 minutes including registration for the meeting, was not unreasonable and was secondary to the main purpose. The Panel therefore ruled no breach of the Code.

The Panel did not consider that the arrangements failed to maintain high standards and no breach of the Code was ruled.

An article entitled 'Drug giants court NHS nurses with luxury hotel breaks' in The Sunday Times criticised the activities of, *inter alia*, GlaxoSmithKline UK Limited. In accordance with established practice the matter was taken up by the Director as a complaint under the Code.

COMPLAINT

The article stated that GlaxoSmithKline had held a dinner for nurses at a four-star hotel to discuss diabetes treatment. The company made medicines to treat the condition.

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

RESPONSE

GlaxoSmithKline stated that it adhered to both the spirit and letter of the Code with regard to hospitality provided to health professionals at company sponsored meetings. The company had robust internal review procedures to ensure that all sponsored meetings had a clear educational content, that hospitality was secondary to the nature of the meeting and that the level of hospitality offered was appropriate and not out of proportion to the occasion. The invitation and arrangements for this meeting received appropriate appraisal and certification. Invitees were from a list of local nurses involved in the care of diabetics in primary care.

In contrast to the report in The Sunday Times of 'a dinner for nurses' this meeting, which took place in October 2004, was an educational meeting of high standard with an independent speaker. There was a modest buffet dinner that was secondary to the educational content, and was at a level consistent with what the participants might pay for themselves.

The meeting started at 7.30pm with a buffet dinner. The speaker was introduced by the chairman of the meeting at 8pm and spoke for one hour before taking questions. The meeting itself was held in a private

room at the hotel, with the buffet served away from the public areas. The educational content was entirely appropriate for an evening meeting. The speaker, a general practitioner and an independently recognised UK authority on the primary care management of type 2 diabetes, talked about a target based approach to diabetes management in primary care.

The cost of the buffet was £1067.50 (quoted per attendee price of £15.25 for 70 attendees, final attendee number 39) and no alcohol was served; room hire for the event was £250. Given that this was a meeting for nurse specialists this was an entirely appropriate level of entertainment which was relevant to the educational content of the meeting.

No travel costs or other expenses were paid for this meeting, there was no use of leisure facilities by attendees and all attendees departed soon after the 9pm meeting close.

GlaxoSmithKline submitted that with regard to Clause 9.1 that 'High standards must be maintained', the invitation and meeting plan were submitted for internal review and were certified. The meeting met acceptable educational standards and the hospitality was modest, clearly secondary to the meeting itself and at a level that the participants might pay for themselves. With regard to Clause 19.1, GlaxoSmithKline submitted that a 30 minute period was allowed for registration and a self-service hot buffet. This was followed by a one hour talk following which attendees departed. Hospitality was clearly given as secondary to the educational meeting. The 30 minutes for registration and the self-service buffet was the minimum time that could be allowed for this purpose and made up around one third of the total meeting time. The per-attendee price quoted by the hotel of £15.25 was clearly not out of proportion to the attendees or occasion. All attendees were health professionals involved in the care of type 2 diabetics.

GlaxoSmithKline confirmed that in its opinion there was no breach of Clauses 2, 9.1 or 19.1.

In response to a request for further information GlaxoSmithKline stated that when representatives arranged catering for an educational meeting it was customary to estimate the number of attendees when making contractual arrangements with a hotel. In this case the representative estimated that there would be 70 attendees at the meeting, representing a cost per head of £15.25. Unfortunately attendance was below the contracted level, hence based on the 39 attendees the cost per head was £27.37. Thus the quality of the meal was typical of one costing £15.25, yet the actual cost was £27.37 per head. GlaxoSmithKline confirmed that this cost included non-alcoholic drinks.

PANEL RULING

The Panel noted that Clause 19.1 of the Code permitted companies to provide appropriate hospitality to members of the health professions and appropriate administrative staff in association with scientific and promotional meetings. Hospitality must be secondary to the purpose of the meeting and the level of hospitality offered must be appropriate and not out of proportion to the occasion. The costs incurred must not exceed the level which recipients would normally adopt if paying for themselves. It must not extend beyond members of the health professions or appropriate administrative staff. The supplementary information stated that the impression created by the arrangements must be borne in mind.

The Panel noted that the meeting started at 7.30pm with a buffet dinner. The speaker, a GP who was an authority on the primary care management of type 2 diabetes, spoke for approximately an hour on a target based approach to primary care diabetes management.

The meeting was held in a private room. The audience was nurse specialists and a few GPs. The cost of the buffet was £15.25 although the actual per head cost was £27.37 due to the difference between the numbers expected and those actually attending. No travel expenses were paid and attendees departed shortly after the close at 9pm.

The Panel considered that the hospitality was secondary to the main purpose of the meeting. The level was appropriate and not out of proportion to the occasion. Half an hour was allowed for registration and the buffet before the presentation started. The cost of £27.37 per delegate was not unreasonable although the Panel considered that it was on the limits of the level that the recipients would normally pay if they were paying for themselves. The presentation would be relevant to specialist nurses in primary care although its length, one hour plus questions, was on the limits of acceptability.

With regard to the points raised in The Sunday Times article, the Panel noted that the Code and UK law allowed medicines to be promoted to health professionals and this would include nurses. Such activity had to comply with the Code.

Taking all the circumstances into account the Panel considered that on balance the meeting was acceptable. It had a clear educational content that was relevant to the audience. The hospitality, which lasted 30 minutes including registration for the meeting, was not unreasonable and was secondary to the main purpose. The Panel therefore ruled no breach of Clause 19.1 of the Code.

The Panel did not consider that the arrangements failed to maintain high standards and no breach of Clause 9.1 was ruled. The arrangements were also ruled not to breach Clause 2 of the Code

Proceedings commenced 28 February 2005

Case completed 27 April 2005

CASE AUTH/1685/2/05

JANSSEN-CILAG v LILLY

Strattera journal advertisements

Janssen-Cilag complained about three Strattera (atomoxetine) journal advertisements, one of them abbreviated, issued by Lilly. Strattera was indicated for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children aged 6 years and older and in adolescents as part of a comprehensive treatment programme. Janssen-Cilag marketed Concerta XL (methylphenidate).

Janssen-Cilag alleged that the claim 'Comparable to OROS methylphenidate in medication-naïve patients' was made in isolation and was not balanced with information from the whole of the cited study (Michelson *et al* 2004) which showed that Oros methylphenidate had significantly superior efficacy on the ADHD rating scale. The study was initially powered to compare the two treatments on the total study population, the subset of medication-naïve patients was too small for a statistically significant difference to be shown. Any conclusion that there was no difference between the two treatments or that they were comparable was spurious. Janssen-Cilag alleged that the claim was a selective representation of a subset of data that was misleading and not a fair and balanced representation of the totality of available data.

The Panel noted that Michelson *et al* was an oral presentation of data from the acute treatment phase (6 weeks) of an 8 month study which compared the response to Strattera and Oros methylphenidate for all patients. The protocol referred to the analysis of specific subgroups including, *inter alia*, stimulant-naïve patients. The sample size was based on 90% power to determine non-inferiority to within 15% for the all patient response analysis, ie the primary comparison. The study presentation was silent on whether the subgroup analysis was so powered. The difference between Strattera and Oros methylphenidate in the mean reduction in ADHD rating scale total score was p=0.015 (all patients) and p=0.253 (stimulant-naïve patients) in favour of Oros methylphenidate. The Panel noted Lilly's submission that these results represented only a 1.8 point difference between the two treatments in the stimulant-naïve patients. Further that a clinical comparison was being made rather than a claim based on statistical significance. The Panel considered that the result, although showing no statistically significant difference between Strattera and Oros methylphenidate, did not unequivocally prove comparable efficacy as suggested by the claim in question. On the limited data available with regard to the design of Michelson *et al* there was no way of knowing the statistical power of the results of the subgroup analyses. The Panel considered that the claim was misleading as alleged. Breaches of the Code were ruled.

Janssen-Cilag stated that in Michelson *et al* Strattera was dosed twice daily. The only reference to dose within the abbreviated advertisement was the third bullet point which read, '24-hour effectiveness with once-daily dosing in children and adolescents'. The reader would therefore assume that once daily Strattera had comparable efficacy to Oros methylphenidate in medication-naïve patients. It should have been made clear that in Michelson *et al* Strattera was given twice daily, failure to do so made the claim 'Comparable to OROS methylphenidate in medication-naïve patients' misleading.

The Panel noted that Section 4.2 of the Strattera summary of product characteristics (SPC) stated that it could be administered as a single daily dose. Patients who did not achieve a satisfactory clinical response (tolerability or efficacy) might benefit from taking it as twice daily in evenly divided doses. Michelson *et al*, administered Strattera (0.8-1.18mg/kg/day) as a divided twice daily dose. The Panel noted that the only reference to dose in the advertisement appeared in the third bullet point '24-hour effectiveness with once-daily dosing in children and adolescents'. The Panel considered that readers might thus wrongly assume that the 'Comparable efficacy to OROS methylphenidate in medication-naïve patients' was achieved with once-daily dosing of Strattera. The claim was misleading on this point as alleged and a breach of the Code was ruled.

Janssen-Cilag noted that the heading to each advertisement, '24-hour relief from ADHD symptoms', was referenced to the Strattera SPC and to a poster presentation (Kelsey *et al* 2003 since published as Kelsey *et al* 2004) which showed significant reductions for 2 of the 3 morning items. The authors urged caution however with regard to the interpretation of their results because the revised parent rating scale used to measure morning effectiveness was new and some of its characteristics had not been studied. Conversely Michelson *et al* 2002 did not show any significant differences between Strattera once daily and placebo on early morning behaviour.

Before February 2005 the Strattera SPC stated: *'When Strattera was administered as a single dose; therapeutic benefit persisted throughout the day'*. 'Throughout the day' implied from morning to night and was therefore not synonymous with a claim of 24 hour efficacy. Janssen-Cilag thus did not consider that this statement substantiated the claim and noted that in any event it had recently been removed from the SPC. Janssen-Cilag alleged that a claim of 24-hour effectiveness did not accurately reflect the totality of the data available.

The Panel noted that Sutton *et al* (a poster presentation) assessed the validity, reliability and responsiveness of the rating scale used by Kelsey *et al* and concluded that although it was acceptable there were limitations which would justify additional work on it. As it was completed after the child went to bed ratings for the morning items might be subject to recall bias or influenced by the child's behaviour during that day or in the evening. In addition morning items did not specify whether they described a child's behaviour before or after receiving morning medications.

In Kelsey *et al* (2004) the total score and the evening and morning subscales showed statistically significant improvements from baseline to endpoint demonstrating effectiveness in behaviour during morning and evening hours. The authors stated that the results should be interpreted cautiously and noted the short duration of the study (8 weeks) limited the ability to make assumptions regarding, *inter alia*, the long term efficacy of Strattera once patients had achieved a satisfactory initial response. The authors concluded that the data suggested a potential advantage of Strattera, compared with stimulant, in that it might provide all-day symptom relief for children that lasted into the evenings and early mornings as soon as the first day of treatment.

The Panel noted that the claim '24-hour relief from ADHD symptoms' headed a photograph of two young boys happily eating breakfast with a woman, presumably their mother, in the background with a newspaper in hand and smiling. The only dose frequency referred to in the advertisements was 'once daily'. In the context in which it appeared the Panel considered that the claim was bold and unequivocal. Readers would assume that the photograph depicted the domestic scene that might be expected from once daily Strattera. In that regard the Panel noted the morning results of Michelson *et al* (2002) (ie no statistically significant difference between Strattera and placebo) and the cautious comments of Kelsey *et al*. The Panel considered that the claim overstated the totality of the data and was misleading in that regard. A breach of the Code was ruled which was upheld on appeal by Lilly.

Janssen-Cilag complained about three journal advertisements for Strattera (atomoxetine) issued by Lilly, an abbreviated advertisement (ref AMX352), which appeared in MIMS and two full advertisements (refs AMX190 and AMX312) which had been widely published in the medical press. Correspondence between the parties had failed to resolve the matter.

Strattera was indicated for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children aged 6 years and older and in adolescents as part of a comprehensive treatment programme. Janssen-Cilag supplied a competitor, Concerta XL (methylphenidate).

A Abbreviated Advertisement

1 Claim 'Comparable to OROS methylphenidate in medication-naive patients'

This claim appeared as the second of three bullet points. A closely similar claim 'Comparable efficacy to OROS methylphenidate in medication-naïve patients' also appeared in one of the full advertisements (ref AMX312) referenced to Michelson *et al* (2004).

COMPLAINT

Janssen-Cilag alleged that the claim 'Comparable to OROS methylphenidate in medication-naïve patients' was made in isolation and was not balanced with information from the whole of Michelson *et al* which demonstrated that Oros methylphenidate had significantly superior efficacy on the ADHD rating scale. The study was initially powered to compare the two treatments on the total study population, a subset analysis of medication-naïve patients had insufficient numbers for a statistically significant difference to be demonstrated. Therefore any conclusion that there was no difference between the two treatments or that the two treatments were comparable was spurious. Use of the statement in isolation was a highly selective presentation of the data.

In addition, Kemner *et al* (2004) compared Concerta XL with Strattera in a randomised controlled study and also showed a significant difference between the two treatments in favour of Concerta XL on the ADHD rating scale.

In summary the claim at issue was a selective representation of a subset of data that was misleading and not a fair and balanced representation of the totality of available data. Janssen-Cilag alleged breaches of Clauses 7.2 and 7.3 of the Code.

RESPONSE

Lilly noted that Michelson *et al*, a double blind, placebo-controlled comparison of atomoxetine, Oros methylphenidate, and placebo, was a non-inferiority comparison of the efficacy of atomoxetine and Oros methylphenidate in 516 patients aged 6-16 years who met the DSM-IV diagnosis for ADHD as measured by the ADHD rating scale.

The acute phase of the study (study period II) was a 6-week, double blind, placebo-controlled, parallel design that allowed investigators to adjust dose, based on clinical response. The dose range for Oros methylphenidate was 18, 36, or 54mg/day and for atomoxetine was 0.8, 1.2, or 1.8mg/kg/day in two divided doses. The sample included both stimulant-naïve patients and those who had previously had a good response to such therapy; importantly it excluded patients who had not responded to stimulants or who were unable to tolerate them because of adverse effects.

Lilly reproduced a barchart from Michelson *et al* which illustrated results from the all-patient group demonstrating that Strattera and Oros methylphenidate were both highly efficacious treatments for ADHD. For consistency with previous communications, the barchart included p values although strictly speaking these were unnecessary given that this was a non-inferiority comparison and that Lilly made a clinical rather than a statistical comparison. The chart showed that in the stimulant-naïve subgroup the mean reduction in ADHD rating scale total symptom score was 17.9 points in the Strattera group and 19.7 points in patients treated with Oros methylphenidate, a difference of 1.8 points in favour of Oros methylphenidate.

Lilly noted that the overall analysis group consisted of two distinct subgroups: prior stimulant users who were known to tolerate and benefit from such therapy and stimulant-naïve patients. The study was powered to assess the whole group and both distinct subgroups were pre-specified analyses in the protocol. For clarity, the abbreviated advertisement made the claim 'Comparable to OROS methylphenidate' only in

relation to a medication-naïve subset. ADHD was a heterogenous condition and individual patients responded differently to different treatments. The claim at issue made the distinction that if a patient was a medication-naïve then the results for Strattera and Oros methylphenidate were similar.

In this regard, the claim at issue was meant to be a selective representation of a subset of data. It was clear that this specific subgroup was being referred to and there was no inference that this claim could be applied to other groups in the study. Hence the claim was not misleading and there was no need to refer to other data from the study. Lilly thus denied breaches of Clauses 7.2 and 7.3 of the Code.

Lilly submitted that the word 'comparable' was not a statistical term and therefore studies could not be powered to demonstrate comparability; the statistical significance of the results was thus irrelevant. The term was chosen to emphasise clinical comparability of the two medications in treating the core symptoms of ADHD as measured by the ADHD rating scale.

The ADHD rating scale was a well-validated, recognised, 18-item questionnaire, rated by investigators on parent questioning. For each question the investigator scored from 0, for no symptoms being present, to 3, for symptoms being present very often. The total ADHD rating scale score therefore had a range of 0 to 54, and small differences in actual score (eg 1.8 points in the stimulant-naïve group), whether or not statistically significant, were certainly not clinically relevant within the context of a child with ADHD. For example, a difference of two points might simply equate to scoring a symptom's presence as being 'often' as opposed to 'very often' on two questions of the 18-item scale.

The term 'comparable,' was carefully chosen to appropriately describe the data. The Oxford Dictionary defined 'comparable' as: 'Able to be likened to another; similar; of equivalent quality; worthy of comparison'. With this definition in mind, a small 1.8 point difference in ADHD rating scale between the two treatment groups, whether or not statistically significant, was minor and made little difference clinically. Lilly believed that it was thus acceptable to state that the two treatments were 'comparable'. As it was quite clearly stated that this was the 'medication-naïve' patient group and made no statements about other patient groups, Lilly disagreed with Janssen-Cilag's assertion that 'Comparable to OROS methylphenidate in medication-naïve patients' was a misleading representation of the totality of available data.

Lilly noted that in intercompany correspondence Janssen-Cilag had stated that Kemner *et al* had demonstrated the superiority of Oros methylphenidate to atomoxetine. As discussed above Lilly had not made a representation of all patient groups, only the medication-naïve subgroup. As Kemner *et al* had no reference to an analysis of this subgroup, it was not relevant to the complaint. Regardless of the relevance of the study to the complaint, Lilly was concerned that the design of the study demonstrated its unsuitability as a comprehensive comparator study. Lilly listed detailed concerns in this regard.

Lilly noted that the National Institute for Health and Clinical Excellence (NICE) was currently evaluating all ADHD medicines for children and adolescents. On 11 March 2005 it published the Appraisal Consultation Document, an initial, comprehensive assessment of all the available efficacy and safety data, and economic modelling of the costs of the different treatments. Section 4.3.2 of the document stated:

> 'The Committee considered the evidence on clinical effectiveness and concluded that methylphenidate, atomoxetine and dexamfetamine are effective in controlling the symptoms of ADHD. Given the large variations in measures of efficacy used across trials, the variable reporting of adverse events, and the lack of long-term studies, the Committee was not able to differentiate between the drugs on the grounds of clinical effectiveness'

Whilst the NICE appraisal document was not final guidance, the review of clinical effectiveness was unlikely to change unless significant new data became available. Final guidance was expected later in 2005.

In summary Lilly considered that the claim at issue was fair, balanced and an appropriate representation of the data; it was not misleading and Lilly denied breaches of Clauses 7.2 and 7.3 of the Code.

PANEL RULING

The Panel noted that Michelson *et al* (2004) was an oral presentation delivered at an academic psychiatry meeting. The Panel had been given copies of the slides used. In his presentation Michelson presented data from the acute treatment phase (6 weeks) of an 8 month study which compared the response to Strattera and Oros methylphenidate for all patients. The protocol – specified analysis provided for the analysis of specific subgroups including, *inter alia*, stimulant-naïve patients. The sample size was based on 90% power to determine non-inferiority to within 15% for the all patient response analysis, ie the primary comparison. The study presentation was silent on whether the subgroup analysis was so powered. Strattera and Oros methylphenidate were each significantly superior to placebo in relation to the mean reduction in the ADHD rating scale for all patients, prior stimulant users and stimulant-naïve patients. The difference between Strattera and Oros methylphenidate in the mean reduction in ADHD rating scale total score was p=0.015 (all patients), p=0.038 (prior stimulant users) and p=0.253 (stimulant-naïve patients) in favour of Oros methylphenidate.

The Panel noted Lilly's submission that with regard to the mean reduction in ADHD rating scale total symptom score, there was only a 1.8 point difference between Strattera and Oros methylphenidate in stimulant-naïve patients (p=0.253). Further that a clinical comparison was being made rather than a claim based on statistical significance. The Panel considered that the result, although showing no statistically significant difference between Strattera and Oros methylphenidate, did not unequivocally prove comparable efficacy as suggested by the claim in question. On the limited data available with regard to the design of Michelson *et al* there was no way of knowing the statistical power of the results of the

subgroup analyses. The Panel considered that the claim was misleading as alleged. Breaches of Clauses 7.2 and 7.3 were ruled.

A2 Misleading with respect to dosage

COMPLAINT

Janssen-Cilag stated that in Michelson *et al* Strattera was dosed twice daily. The only reference to dose within the abbreviated advertisement was the third bullet point, '24-hour effectiveness with once-daily dosing in children and adolescents'. The reader would therefore assume that Strattera taken once daily had comparable efficacy to Oros methylphenidate in medication-naïve patients. As the dose of Strattera in Michelson *et al* was given twice daily this should have been made clear. Failure to do so made the claim 'Comparable to OROS methylphenidate in medication-naïve patients' misleading in breach of Clause 7.2 of the Code.

RESPONSE

Lilly disagreed that the abbreviated advertisement misled with respect to frequency of dosage. The advertisement was headed '24-hour relief from ADHD symptoms'. The four bullet points beneath referred to this title and not to each other. The bullet point 'Comparable to OROS methylphenidate in medication-naive patients' was not within a second claim of '24-hour effectiveness with once-daily dosing in children and adolescents' as had been suggested. It was clear from the advertisement that the bullet points referred to the title and therefore the claim was not misleading as alleged. Lilly denied a breach of Clause 7.2.

PANEL RULING

The Panel noted that Section 4.2 of the Strattera summary of product characteristics (SPC) stated that it could be administered as a single daily dose. Patients who did not achieve a satisfactory clinical response (tolerability or efficacy) might benefit from taking it as twice daily evenly divided doses.

The Panel noted that Michelson *et al*, administered Strattera in the dose range 0.8-1.18mg/kg/day as a divided twice daily dose. The Panel noted that the only reference to dose in the advertisement appeared in the third bullet point '24-hour effectiveness with once-daily dosing in children and adolescents'. The Panel considered that a reader might thus assume that the 'Comparable efficacy to OROS methylphenidate in medication-naïve patients' was achieved with once-daily dosing of Strattera and that was not so. The claim was misleading on this point as alleged. A breach of Clause 7.2 was ruled.

B Claim '24-hour relief from ADHD symptoms'

This claim headed each advertisement.

COMPLAINT

Janssen-Cilag stated that the claim had been referenced to the Strattera SPC and to a poster presentation (Kelsey *et al* 2003 since published as Kelsey *et al* 2004). Within this publication significant reductions were seen for 2 of the 3 morning items (using the daily parent ratings of evening and morning behaviour – revised (DPREMB-R) scale). The study authors noted however that these results should be interpreted cautiously, because the instrument used to measure morning effectiveness was new and its psychometric characteristics had not been studied. Conversely, Janssen-Cilag noted that Michelson *et al* 2002, which used a parent-rated daily diary (DMREMB), did not demonstrate any significant differences between Strattera once daily and placebo on early morning behaviour.

Before February 2005 the Strattera SPC stated: 'When Strattera was administered as a single dose; therapeutic benefit persisted throughout the day'. 'Throughout the day' implied from morning to night and was therefore not synonymous with a claim of 24 hour efficacy (ie efficacy that lasts throughout the first day and into the next day). Janssen-Cilag did not consider that the SPC substantiated this claim – a once daily dosage did not equate with '…therapeutic benefit persisted throughout the day'.

Furthermore there had been an important change made to the Strattera SPC (February 2005). At a recent revision of the SPC the statement 'When Strattera was administered as a single dose; therapeutic benefit persisted throughout the day' had been removed.

Claims must be balanced, fair, objective and unambiguous and must be based on an up-to-date evaluation of all the evidence and reflect that evidence clearly. Given the disparity of the available data regarding the efficacy of Strattera given once daily in the morning (ie one study showing effectiveness and one not), and the recent removal of the statement 'When Strattera was administered as a single dose; therapeutic benefit persisted throughout the day' from the SPC, a claim of 24-hour effectiveness did not accurately reflect the totality of the data available and was therefore in breach of Clause 7.2 of the Code.

RESPONSE

Lilly denied that the claim was not balanced, fair, objective, unambiguous and based on an up-to-date evaluation of all the evidence.

At the time that the advertisements were approved for use, the May 2004 version of the SPC applied, Section 5.1 (Pharmacodynamic properties) of which stated: 'Strattera was effective as a single daily dose and as a divided dose administered in the morning, and late afternoon/early evening. Strattera administered once daily demonstrated statistically significantly greater reduction in severity of ADHD symptoms compared with placebo as judged by teachers and parents. When Strattera was administered as a single dose, therapeutic benefit persisted throughout the day'.

As Strattera was being reviewed by individual member states throughout Europe via the mutual recognition process, there was the possibility that changes would need to be made to the UK SPC. Very recently (January 2005) the above statement was amended to read: 'Strattera was effective as a single

daily dose and as a divided dose administered in the morning and late afternoon/early evening. Strattera administered once daily demonstrated statistically significantly greater reduction in severity of ADHD symptoms compared with placebo, as judged by teachers and parents.'

Lilly disagreed with Janssen-Cilag's view that the phrase 'therapeutic benefit persisted throughout the day' did not substantiate the claim of 24-hour efficacy. When the phrase was read in the context of Section 5.1 of the SPC (above), it was clear that Strattera had 24-hour efficacy from a single daily dose and that 'throughout the day' should be understood as covering a 24-hour period. Although the phrase 'therapeutic benefit persisted throughout the day' had been removed from the revised SPC, this did not mean that the claim of 24-hour relief of symptoms could not be supported. The claim could clearly be substantiated in any event by the sections of the SPC stating 'Strattera was effective as a single daily dose' and 'Strattera administered once daily demonstrated statistically significantly greater reduction in ADHD symptoms compared to placebo'. Lilly considered that both the May 2004 and the January 2005 SPC were in keeping with its claim for 24-hour efficacy.

It was well known that the observed clinical effect of stimulant medication wore off as the day progressed and once the efficacy of Strattera had been established in treating the core symptoms of ADHD it was considered appropriate to make an assessment of the control of ADHD behaviours in the late evenings and early mornings (prior to receiving that day's dose of Strattera). This was done in an exploratory manner in Michelson *et al* (2002), and more rigorously by Kelsey *et al*.

The scale utilised was the DPREMB which was a secondary outcome measure in Michelson *et al* (2002). Following on from this initial study, during the process of validating the scale, it was modified to the DPREMB Revised (DPREMB-R), which was used in the poster (Kelsey *et al*) which had now been published in a peer reviewed major journal, as Kelsey *et al* (2004). The validity, reliability and responsiveness of the DPREMB-R had been demonstrated (Sutton *et al* 2003).

Although the exploratory Michelson *et al* (2002) did not find a statistically significant difference on the morning items of the DPREMB scale, Kelsey *et al* did. Lilly considered Kelsey *et al* was the more reliable paper because to be included in the DPREMB-R weekly calculation, at least 4 of the 5 baseline records and 6 of 7 records in one of the four weeks after baseline must have been completed. These criteria ensured that an accurate assessment of the child's daily behaviour was captured. Furthermore the analysis included baseline DPREMB-R as a covariate whereas the exploratory Michelson *et al* (2002) did not. Thus Kelsey was a more robust analysis. Indeed, a major conclusion of Kelsey *et al* was around 24-hour symptom relief ie 'the most striking finding of this study is the confirmatory evidence that once-daily dosing in the morning is associated with significant symptom reduction that persists into the evening and into the morning hours'.

The Medicines and Healthcare products Regulatory Agency (MHRA) recently issued guidance on the use of 24-hour relief claims in advertisements. The guidance stated that 'For 24 hour relief, data must show clinical effect over the 24 hour period'. Kelsey *et al* (2004) showed clinical effect over a 24 hour period.

In summary, Lilly considered that the claim that Strattera provided '24 hour relief from ADHD symptoms' was balanced, fair, objective and unambiguous, and was based on an up-to-date evaluation of all evidence. Lilly denied breaches of Clauses 7.2 and 7.3 of the Code.

PANEL RULING

The Panel noted Lilly's submission about the Strattera SPC and Michelson *et al* (2002). Michelson *et al* (2002) did not demonstrate any differences between once daily Strattera and placebo on DPREMB early morning behaviour but did suggest medicine specific effects on two evening items (inattentive symptoms and difficulties settling at bedtime). A post-hoc comparison found that the number of evening items for which the mean decrease was greater with Strattera than with placebo was higher than expected by chance ($p < 0.04$). The study authors noted however that the clinical importance of this finding and its replicability required further study.

The Panel noted that Sutton *et al* (a poster presentation) was designed to assess the validity, reliability and responsiveness of the DPREMB-R scale for ADHD and concluded that it was acceptable in this regard but noted there were limitations which would justify additional work on the scale. As it was completed in the evening after the child went to bed ratings for the morning items might be subject to recall bias, influenced by the child's behaviour during that day and by ratings of evening items. In addition morning items did not specify whether they described a child's behaviour before or after receiving morning medications.

In Kelsey *et al* (2004) the DPREMB-R total score and the evening and morning subscales showed statistically significant improvements from baseline to endpoint demonstrating effectiveness in behaviour control during both morning and evening hours. The authors stated that the results should be interpreted cautiously because the instrument was new and its psychometric characteristics had not been studied. The short duration of the study (8 weeks) limited the ability to make assumptions regarding, *inter alia*, the long term efficacy of Strattera once patients had achieved a satisfactory initial response. In their conclusions the authors stated that the data suggest a potential advantage of Strattera, compared with stimulant, in that it **might** (emphasis added) provide all-day symptom relief for children that lasted into the evenings and early mornings as soon as the first day of treatment.

The Panel noted that the claim '24-hour relief from ADHD symptoms' headed a photograph of two young boys happily eating breakfast with a woman, presumably their mother, in the background with a newspaper in hand and smiling. The only dose frequency referred to in the advertisements was 'once daily'. In the context in which it appeared the Panel considered that the claim was bold and unequivocal. Readers would assume that the photograph depicted

the domestic scene that might be expected from once daily Strattera. In that regard the Panel noted the morning results of Michelson *et al* (2002) and the cautious comments of Kelsey *et al*. The Panel considered that the claim overstated the totality of the data and was misleading in that regard. A breach of Clause 7.2 was ruled.

APPEAL BY LILLY

Lilly submitted that although the Panel appeared to have accepted there was some evidence of 24-hour efficacy from a once daily morning dose of Strattera (ie efficacy through the evening and into the next morning), the ruling was unclear as to whether the use of the phrase alone was misleading as alleged by Janssen-Cilag. Lilly assumed that the ruling was specifically made in relation to the context of the statement with the picture, and that the data, and the SPC (stating that 'Strattera was effective as a single daily dose' and 'Strattera administered once daily demonstrated statistically significantly greater reduction in ADHD symptoms compared with placebo') continued to support a claim of 24-hour effect for Strattera.

Lilly noted that Michelson *et al* looked at persistence of effect of atomoxetine, and used the Lilly-devised DPREMB scale to assess behaviours associated with ADHD in late evenings (ie approximately 12 hours after a morning dose of Strattera), and early mornings (approximately 24 hours after a dose of Strattera). Nine of the thirteen items on the questionnaire specifically looked at evening behaviours, and four of the items assessed morning behaviours. The study focused on efficacy persisting into the late evenings, when children had returned home from school (thus more items on the DPREMB related to symptoms in the evenings rather than symptoms the following morning). This was clinically important, as these were times when children did their homework and sat down with the family at mealtimes. Michelson *et al* demonstrated that two of the nine evening items were statistically significant and six of the nine evening items favoured Strattera. None of the morning items were statistically significant, although three favoured atomoxetine. The author stated: 'Perhaps the most striking finding of this study is that despite the relatively short plasma half life of the atomoxetine (about 4 hours for most patients), once daily dosing in the morning was associated with effects that persist into the evening'.

Lilly noted that Kelsey *et al* also used a slightly revised DPREMB scale to further explore the persistent effects of Strattera after a once daily morning dose. The revision removed the assessment of 'irritability' from the evening and morning items as this symptom was not considered to be in keeping with the core features of ADHD. Thus there were eight evening items and three morning items. In addition an assessment of the total DPREMB-R score was made and a separate evening subscore total (incorporating all evening items), and morning subscore total (incorporating all morning items). This study built on the preliminary data in Michelson *et al* and was designed to be more robust in its assessment of persistence of effect in that: to be included in the Kelsey *et al* DPREMB-R weekly calculation, at least 4 of the 5 baseline records and 6 of 7 records in one of the four weeks after baseline must have been completed. These criteria ensured that an accurate assessment of the child's daily behaviour was captured. Furthermore the analysis included baseline DPREMB-R as a covariate whereas Michelson *et al* did not. Thus Kelsey *et al* was a more robust analysis.

Lilly noted that in Kelsey *et al*, five of the eight individual evening items were statistically significant, as was the evening item total subscore; two of the three morning items were statistically significant, as was the morning item total subscore. The author stated: 'The most striking finding of this study is the **confirmatory** evidence that once-daily dosing in the morning is associated with significant symptom reduction that persists into the evening and **into the morning hours**' (emphasis added).

Lilly noted that Sutton *et al* (2003) evaluated the validity, reliability and responsiveness of the DPREMB-R utilising data from Kelsey *et al* and Michelson *et al*. The author stated in the conclusion: 'Clinical data results indicate the DPREMB-R is a valid, reliable, and responsive scale for collecting effects of treatment on morning and evening activities often impaired by ADHD' and 'There are limitations that would justify additional work on the DPREMB-R'. Lilly submitted that such limitations related to the fact that there was as yet limited clinical and research experience with the scale.

Since the Panel ruling, the results of another two studies contributed further evidence of 24-hour efficacy. LYCC, a clinical study, used similar methodology to the two previous 24-hour efficacy studies, but used a different scale to assess 24-hour duration of effect, and a pharmacokinetic study (LTBC) demonstrated that once steady state had been reached atomoxetine was present in the cerebrospinal fluid 24-hours after a dose. Details of each study were provided.

Lilly submitted that Michelson *et al* had provided preliminary evidence for 24-hour efficacy, and that Kelsey *et al* had built on this and contributed more robust evidence.

Lilly submitted that the Panel had misinterpreted one of the conclusions of Kelsey *et al* as mentioned in its ruling. The Panel referred to one of the conclusions in Kelsey *et al*: 'The data also suggest a potential advantage of Strattera, compared with stimulants, in that it **may** provide all-day symptom relief for children that lasts into the evenings and early mornings as soon as the first day of treatment' (emphasis added). Elsewhere in the paper, Kelsey *et al* stated that 'The most striking finding of this study is the **confirmatory** evidence that once-daily dosing in the morning is associated with significant symptom reduction that persists into the evening and **into the morning hours**' (emphasis added) and 'The results of the present study are consistent with those findings (ie of previous atomoxetine studies) and extend them by demonstrating significant drug-specific effects persisting not only into the evening hours **but also into the morning hours** [emphasis added]. This is also the first study to demonstrate significant efficacy of atomoxetine as soon as the first day of treatment'.

Lilly noted that the Panel had considered that Kelsey *et al* had made a cautious comment about 24 hour efficacy. Rather, the above quotations made it clear that Kelsey *et al* was not expressing doubt that atomoxetine provided symptom relief that lasted into the evenings and early mornings – the author was stating that such relief **might** commence as soon as the first day of treatment.

Lilly noted that the MHRA had recently issued guidance on the use of 24-hour relief claims ie 'For 24-hour relief, data must show clinical effect over the 24-hour period' (Mail 141 January/February 2004). The guidance also referred to the use of 24-hour claims in advertising: 'Claims in advertising may be supported by the SPC or by evidence of onset or duration of relief…'.

Lilly submitted claims that a claim of 24 hour relief was supported by Section 5.1 of the Strattera SPC which stated that 'Strattera was effective as a single daily dose' and 'Strattera administered once daily demonstrated statistically significantly greater reduction in ADHD symptoms compared with placebo'. In addition Kelsey *et al* provided evidence of the duration of relief by confirming clinical effect over a 24 hour period.

Lilly stated that on 25th June 2004, shortly after Strattera received a marketing authorization the MHRA had requested the references for one of the advertisements that was the subject of this appeal and included the claim '24 hour continuous symptom relief with once daily dosing in children and adolescents' in the context of the picture discussed.

Lilly supplied the required references to the MHRA, including data from Kelsey *et al* (although as yet this had not been published as a formal journal article, but as a poster presentation). Following the MHRA's considered review of the information, no adverse comments regarding the advertisement or data were made.

In summary Lilly considered that the claim that Strattera provided '24-hour relief from ADHD symptoms' was a balanced, fair, objective and unambiguous representation of the totality of data available. The company denied a breach of Clause 7.2 of the Code.

COMMENTS FROM JANSSEN-CILAG

Janssen-Cilag noted that Michelson *et al* showed that there was no effect on morning behaviour (approximately 24-hours post-dose) using the Lilly-devised DPREMB scale. This study showed no significant effect with Strattera compared with placebo on any of the items of the DPREMB morning scale (difficulty getting out of bed, difficulty getting ready, arguing/struggling, irritability). The authors concluded that 'comparisons of mean changes on other items and on morning items were not statistically significant', indeed the authors had appeared to express surprise that the effects of Strattera even lasted into the evening. They commented that 'perhaps the most striking finding of this study was that despite the relatively short half life of atomoxetine (about 4 hours for most patients), once daily dosing in the morning was associated with effects that persisted into the evening'. Janssen Cilag considered that this study did not support the bold and unequivocal claim for '24-hour relief from ADHD symptoms'. In fact it showed that there was not 24-hour relief from symptoms.

Kelsey *et al* used the DPREMB-R morning subscore to measure morning efficacy as a secondary efficacy measure. This was a revised version of the scale used in Michelson *et al* from which the irritability item had been removed. The published data from this study stated that: 'Decreases at endpoint in the DPREMB-R morning subscore indicated a significant reduction in symptoms that lasted into the morning. Comparisons of mean changes in the individual items of the DPREMB-R demonstrated significant atomoxetine-specific reductions for … 2 of the 3 morning items.'

Janssen-Cilag noted that Lilly's trials website (www.lillytrials.com, trial 5670, report) revealed data not reported in the final publication. These data showed that there was no consistent significant effect on the total DPREMB-R morning subscore when the results were analysed both on a week by week basis and at endpoint.

The table below from the trial report detailed the repeated measures least square means for each week of the trial.

Least square means for DPREMB-R Morning (table LYBG.4)

Week	*Atomoxetine*	*Placebo*	*Treatment difference*	*P value*
1	2.75	3.09	–0.34	0.070
2	2.5	3.04	–0.54	0.011
3	2.37	2.96	–0.59	0.015
4	2.25	2.57	–0.32	0.263

Janssen-Cilag noted that a significant effect on the morning subscore was only seen at weeks two and three. There was no significant difference at weeks one and four.

Moreover, Janssen-Cilag noted that the table below, also from the trial report, showed that the change on the DPREMB–R morning subscore from baseline to endpoint was also not significant (p=0.066).

Mean change in DPREMB-R by endpoint (table LYBG.6)

	Mean change	*P value*
Atomoxetine	–1.58	0.066 (not significant)
Placebo	–0.95	

Following its analysis of the data in the published paper and in the study report on Lilly's trials website, Janssen-Cilag concluded that Kelsey *et al* did not support the bold and unequivocal claim that Strattera dosed once-daily provided '24-hour relief from ADHD symptoms'.

Janssen-Cilag acknowledged that Sutton *et al* had concluded that the Lilly-devised DPREMB-R was a valid, reliable and responsive scale for collecting effects of treatment on morning and evening activities

often impaired by ADHD. However, the authors conceded that the scale had 'limitations that would justify additional work'. At this time Janssen-Cilag considered that there was no universally accepted or used scale to assess the efficacy of treatments for ADHD symptoms in the morning 24 hours post-dose.

Janssen-Cilag noted that two studies using once-daily dosing were available when the claim in question was made. The results from these studies were Michelson (2002), no significant difference compared to placebo and Kelsey (2004), no consistent significant difference compared to placebo. Thus neither supported the bold and unequivocal claim that Strattera provided '24-hour relief from ADHD symptoms'. The company thus endorsed the Panel's ruling that such a claim was in breach of Clause 7.2 of the Code as it was misleading and not a true representation of the body of evidence.

Janssen-Cilag stated that the MHRA guidance clearly stated that for 24-hour relief claims the data must show clinical effect over the 24 hour period and the product should be for once daily dosing but that a once daily dosing interval alone was insufficient to support a 24-hour claim.

Janssen-Cilag alleged that the data presented did not support efficacy lasting 24 hours.

Janssen-Cilag referred to the statement 'When atomoxetine was administered as a single dose, therapeutic benefit persisted throughout the day', which had been in the Strattera SPC prior to February 2005, and alleged that 'throughout the day' was not synonymous with 24-hour efficacy so did not substantiate a claim for this.

Janssen-Cilag noted that the MHRA had reviewed the data on Strattera in relation to an advertisement which included the claim for continuous 24-hour symptom relief. Janssen-Cilag noted that when the MHRA carried out this review, the Kelsey *et al* data had not been published in a peer-reviewed journal nor was the detailed trial report now available as report 5670 on the Lilly website.

Janssen-Cilag alleged furthermore, that on the basis of past decisions it was aware that MHRA reviews like this had little bearing on subsequent cases of complaints involving the Authority.

In conclusion Janssen-Cilag alleged that the data from the two trials available at the time when the advertisements at issue were created and used had not justified the bold and unequivocal claim for '24-hour relief from ADHD symptoms' in the context of once daily dosing. The Strattera SPC did not support the bold and unequivocal claim for '24-hour relief from ADHD symptoms'.

Janssen-Cilag endorsed the original decision of the Panel that the bold and unequivocal claim for '24-hour relief from ADHD symptoms' in the context of once daily dosing of atomoxetine was in breach of Clause 7.2 of the Code.

APPEAL BOARD RULING

The Appeal Board noted that studies LYCC and LTBC only became available after the Panel ruling. They were not available at the time the advertisement was used nor at the time of the complaint. Thus the Appeal Board disregarded these studies.

The Appeal Board noted that the message from the advertisements at issue was that once daily dosing with Strattera provided '24-hour relief from ADHD symptoms'. This was a bold and unequivocal claim for which the Strattera SPC, Michelson *et al* and Kelsey *et al* had been cited in support.

The Appeal Board noted that when the advertisements had been prepared the Strattera SPC had contained the statement 'When Strattera was administered as a single dose, therapeutic benefit persisted throughout the day'. The Appeal Board noted, however, that 'throughout the day' was ambiguous as it was unclear as to whether it related to waking hours or to 24-hours. In the Appeal Board's view the statement was not a robust enough basis for an unequivocal claim of 24-hour relief; in that regard it was, therefore, irrelevant that the statement had been removed from the Strattera SPC in February 2005.

The Appeal Board similarly considered that neither Michelson *et al* nor Kelsey *et al* provided unequivocal support for the strong claim of 24-hour relief. The mean final dose of atomoxetine in both studies was 1.3mg/kg/day vs a recommended maintenance dose of approximately 1.2mg/kg/day (depending on the patient's weight and available dosage strengths of atomoxetine) (ref Strattera SPC). The SPC went on to state that no additional benefit had been demonstrated for doses higher than 1.2mg/kg/day. Further, the Appeal Board noticed that neither Michelson *et al* nor Kelsey *et al* referred to 24-hour relief of symptoms, using instead phrases such as 'all-day symptom relief' 'symptom relief that lasted not only into the evening hours but also into the morning hours' and 'effects that persisted into the evening'. Morning efficacy outcomes, measured at trough, in both studies were limited. Michelson *et al* failed to show any statistically significant difference in favour of atomoxetine in the morning and Kelsey *et al* only demonstrated significant atomoxetine specific reductions for two out of three morning items. Both studies urged caution as to the interpretation of their results given that the instrument used to assess efficacy (DPREMB or DPREMB-R) was new and they called for further studies to confirm their findings. Both studies also noted that there had been no direct comparisons of atomoxetine taken once daily in the morning with other atomoxetine dosing schedules. In that regard the Appeal Board noted that the Strattera SPC stated that the medicine could be administered as a single dose in the morning; patients who did not achieve a satisfactory clinical response (tolerability or efficacy) when taking Strattera as a single daily dose might benefit from taking it in two evenly divided doses.

The Appeal Board considered that the claim '24-hour relief from ADHD symptoms' was bold, unequivocal and overstated the totality of the data and was misleading in that regard. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful.

Complaint received **28 February 2005**

Case completed **14 July 2005**

CASE AUTH/1686/3/05

GENERAL PRACTITIONER v JANSSEN-CILAG

Promotion of Durogesic to the public

A general practitioner was concerned that an article in the Daily Mail reporting the launch of the Durogesic DTrans (transdermal fentanyl 25mg) patch promoted the product as an alternative to COX-2 inhibitors for chronic backache. The article was headed 'The back pain patch. Relief for millions on the NHS'.

The Panel noted that the relevant press release was entitled 'New treatment and education campaign launched today to address chronic pain of millions in Britain'. Although one statement read 'New Durogesic DTrans represents a significant advance in the treatment of severe chronic pain...' others read 'The Durogesic DTrans matrix patch offers effective, round-the-clock relief from pain...', 'to help the millions of people ... whose lives are blighted by chronic pain' and 'This new breakthrough in patch technology must be seen as a benefit in the management of pain...'. There were few references to pain being anything other than chronic; there was no reference to chronic intractable pain, the licensed indication for Durogesic DTrans.

The press release referred to a National Opinion Poll (NOP) to mark the launch of the campaign in which 53% of those questioned had suffered, or knew of someone else who had suffered ongoing/persistent pain. Janssen-Cilag acknowledged that there was no way of knowing if this pain was chronic intractable pain for which Durogesic DTrans was licensed.

In the 'Notes to Editor' the press release stated that 'Durogesic DTrans... provides reliable pain relief ... for patients with lower back pain, osteoarthritis, rheumatoid arthritis, neuropathic pain, cancer and non-cancer associated pain'. The launch press packs also contained backgrounders entitled 'Chronic Pain Conditions Explained' and 'Chronic Pain' which referred to osteoarthritis (OA), rheumatoid arthritis (RA) and back pain. The document explaining chronic pain conditions referred, *inter alia*, to the use of COX-2 inhibitors, to reduce inflammation and joint pain. A backgrounder 'Opioids for the treatment of chronic pain-past, present and future' referred to the future management of chronic pain and that new developments in opioid delivery systems, such as transdermal patches, enhanced the treatment of pain and opened doors to new clinical situations where these medicines could be effectively used.

The Panel noted that the Durogesic DTrans launch press pack had been issued at a time when there were major concerns about the safety profile of COX-2 inhibitors. Given the tone and content of the press pack the Panel did not consider it unreasonable that some journalists would see Durogesic DTrans as an alternative to COX-2 inhibitors and write an article accordingly.

The Panel did not consider that the material issued to the press to mark the launch of Durogesic DTrans constituted an advertisement to the general public for the product. No breach of the Code was ruled in that regard. However, the Panel considered that the press pack was not balanced with regard to the licensed indications for Durogesic DTrans. Many people with chronic pain, but not intractable chronic pain, would be encouraged to ask their doctors to prescribe Durogesic DTrans in the false belief that such therapy was suitable for them. This was not so. A breach of the Code was ruled. High standards had not been maintained and a further breach of the Code was ruled.

The Panel considered that a press pack which implied that a medicine could be used in a wider patient population than that for which it was authorized was unacceptable. As acknowledged by Janssen-Cilag the press release was misleading. In the Panel's view the resultant newspaper article was thus also misleading and would give false hope to some patients. The Panel considered that such activity brought discredit upon, and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

A general practitioner complained about an article in the Daily Mail, February 2005, which concerned the launch of a Durogesic patch. The article was headed 'The back pain patch. Relief for millions on the NHS'. Durogesic DTrans was a fentanyl transdermal patch supplied by Janssen-Cilag Ltd. Each patch was to be worn continuously for three days.

COMPLAINT

The complainant was concerned that the article promoted Durogesic patches as an alternative to COX-2 inhibitors for chronic backache. The complainant was particularly concerned that Durogesic was a controlled drug; he understood that the 25mcg patch was equivalent to 100mg of morphine daily. In his view it was unethical for this medicine to be promoted in this way in the general press.

When writing to Janssen-Cilag, the Authority asked it to respond in relation to Clauses 2, 9.1, 20.1 and 20.2.

RESPONSE

Janssen-Cilag stated that it had issued two press releases in February, one aimed at the lay press, the other at the medical press, announcing the launch of the Durogesic DTrans fentanyl matrix delivery system. The introductory paragraphs of the press releases made it clear that it was intended that 'the patch would provide reliable pain relief for people with severe chronic pain'. The press releases went on to provide comments from key opinion leaders about potential benefits to be gained from the use of the patch and refered (with permission) to the British Pain Society's recommendations on the use of strong opioids in the management of chronic pain.

The company also used these press releases to launch 'Translating Pain', an educational initiative supported by 'Pain Concern' (an educational charity) which aimed to encourage better communication about

explaining and seeking the most effective treatment for pain relief between patients and their GP. This part of the press releases included a quotation from Pain Concern. The press releases provided background information to a recent National Opinion Poll (NOP) which highlighted the prevalence and impact of chronic pain and views towards treatment. The press releases ended with further quotations from opinion leaders regarding treatment perspectives and about the launch of Durogesic DTrans. The press releases included media contact points, specific 'notes for editors' and appropriate references used within the release itself.

A public relations (PR) agency managed the launch and acted as the link with the media, opinion leaders and Pain Concern. Janssen-Cilag briefed the agency about the launch of the new formulation, and the educational initiative. The launch press pack included: either the medical or lay press release; backgrounders entitled 'Chronic Pain Conditions Explained', 'Chronic Pain', and 'Opioids for the Treatment of Chronic Pain – Past, Present & Future' and the Durogesic DTrans summary of product characteristics (SPC).

Specialist company sales representatives or a senior marketing colleague had visited opinion leaders regarding their interest in principle in joining the launch of the formulation and the educational campaign. The opinion leaders were handed a letter and given a detailed explanation about the campaign launch. The PR agency made all subsequent contact with these clinicians and appropriate preparations for the launch of the campaign were made.

Press releases were circulated to media outlets on 21 February (with an instruction that these were not to be used before 00.01 hours on 23 February). The media was asked to contact the PR agency should interviews with the quoted opinion leaders or further information be required. No press conferences were organised or held. No specific contact after the press release was issued was made with or from the Daily Mail.

It appeared to Janssen-Cilag that the complainant's particular concern was that Durogesic DTrans was being promoted as an alternative to COX-2 inhibitors for chronic backache. Janssen-Cilag regretted that the journalist made this statement in the Daily Mail article, but would also be most concerned if its press release material stated or implied that its product could be used as an alternative in this way.

Janssen-Cilag noted that the main press releases made no mention of Durogesic DTrans acting as an alternative to COX-2 inhibitors. Indeed, the specific referral to the British Pain Society's recommendations regarding the use of strong opioids in the management of chronic pain was intended to ensure that any statements about the use of strong opioids in the management of these conditions were appropriate and evidence-based. The complainant was correct in stating that the Durogesic DTrans 25mcg/h strength was approximately equivalent to 100mg morphine (in fact, 90mg, as used within the SPC). However, launching Durogesic DTrans in this way was not unethical. Janssen-Cilag stressed that the use of the highly regarded British Pain Society's recommendations together with the agreement of opinion leaders in the field and the launch of a novel educational initiative was aimed at highlighting another new treatment that would now be available to prescribers for chronic pain in certain conditions.

In the context of Clause 20.1, and for the rationale explained above, Janssen-Cilag did not accept that the Durogesic DTrans press releases, backed by recognised professional bodies and evidence, constituted advertising to the general public. These were press releases for Durogesic DTrans, which was licensed in chronic intractable pain. The NOP survey information, interesting though it was, gave information related to pain states where there was no certainty that the pain was of the severity included in the indication 'chronic intractable pain'. Accordingly Janssen-Cilag accepted that the presence of the NOP survey information could lead to a misleading interpretation of the information on Durogesic DTrans and hence it conceded a breach of Clause 20.2.

Janssen-Cilag noted, however, that on reading how the Daily Mail journalist had interpreted the press release, it realised how this aspect might be misleading and might imply that Durogesic DTrans was suitable for 'millions'. Janssen-Cilag therefore subsequently created an addendum press release which was issued on the launch day itself (24 February 2005) to the same media outlets that had received the original press release.

In conceding a breach of Clause 20.2, Janssen-Cilag also accepted that high standards in this regard were not maintained at all times and conceded a Clause 9.1 breach.

Whilst conceding that high standards were not maintained in the original press releases, Janssen-Cilag did not consider that the press releases had brought such discredit upon or reduced confidence in the industry to the point where the particular censure of a ruling of a breach of Clause 2 was required. Accordingly, Janssen-Cilag denied a breach of Clause 2.

PANEL RULING

The Panel noted that complaints about articles in the press were judged on the information provided by the pharmaceutical company or its agent to the journalist and not on the content of the article itself.

The press release which had been sent to the lay press was entitled 'New treatment and education campaign launched today to address chronic pain of millions in Britain'. The press release referred to the incidence of chronic pain in the UK and the effect that such pain had on patients' lives. Although one statement read 'New Durogesic DTrans represents a significant advance in the treatment of severe chronic pain...' others read 'The Durogesic DTrans matrix patch offers effective, round-the-clock relief from pain...', 'to help the millions of people ... whose lives are blighted by chronic pain' and 'This new breakthrough in patch technology must be seen as a benefit in the management of pain...'. There were few references to pain being anything other than chronic; there was no reference to chronic intractable pain. In that regard

the Panel noted that the licensed indication for Durogesic DTrans was in the management of chronic intractable pain including that due to cancer.

The press release referred to an NOP survey released to mark the launch of the campaign in which 53% of those questioned had suffered themselves, or knew of someone else who had suffered ongoing/persistent pain. Janssen-Cilag had acknowledged that there was no way of knowing if this pain was chronic intractable pain for which Durogesic DTrans was licensed.

In the 'Notes to Editor' the press release stated that 'Durogesic DTrans... provides reliable pain relief over three full days for patients with lower back pain, osteoarthritis, rheumatoid arthritis, neuropathic pain, cancer and non-cancer associated pain'. The Panel noted Janssen-Cilag's submission that the launch press packs also contained backgrounders entitled 'Chronic Pain Conditions Explained' and 'Chronic Pain'. Both of these documents referred to osteoarthritis (OA), rheumatoid arthritis (RA) and back pain. The document explaining chronic pain conditions referred to the use of COX-2 inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids to reduce inflammation and joint pain. A backgrounder 'Opioids for the treatment of chronic pain-past, present and future' referred to the future management of chronic pain and that new developments in opioid delivery systems, such as transdermal patches, enhanced the treatment of pain and opened doors to new clinical situations where these medicines could be effectively used.

The Panel noted that the Durogesic DTrans launch press pack had been issued at a time when there were major concerns about the safety profile of COX-2 inhibitors. Given the tone and content of the press pack the Panel did not consider it unreasonable that some journalists would see Durogesic DTrans as an alternative to COX-2 inhibitors and write an article accordingly.

The Panel did not consider that the material issued to the press to mark the launch of Durogesic DTrans constituted an advertisement to the general public for the product. No breach of Clause 20.1 was ruled.

Clause 20.2 of the Code required that information about a medicine which was made available to the general public either directly or indirectly 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. The Panel considered, however, that the press pack at issue was not presented in a balanced way with regard to the licensed indications for Durogesic DTrans. Many people with chronic pain, but not intractable chronic pain, would be encouraged to ask their doctors to prescribe Durogesic DTrans in the false belief that such therapy was suitable for them. This was not so, the press pack was thus unbalanced in that regard. The Panel ruled a breach of Clause 20.2. High standards had not been maintained and the Panel ruled a breach of Clause 9.1. Janssen-Cilag had conceded both of these rulings of a breach of the Code.

The Panel noted that a ruling of a breach of Clause 2 of the Code was a sign of particular censure and reserved for such use. The Panel considered that a press pack which implied that a medicine could be used in a wider patient population than that for which it was authorized was unacceptable. As acknowledged by Janssen-Cilag the press release was misleading. In the Panel's view the resultant newspaper article was thus also misleading and would give false hope to some patients. The Panel considered that such activity brought discredit upon, and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

Complaint received **3 March 2005**

Case completed **19 April 2005**

CASES AUTH/1687/3/05 and AUTH/1699/3/05

SCHERING HEALTH CARE v TEVA and AVENTIS

Copaxone detail aid

Schering Health Care complained about a Copaxone (glatiramer acetate) detail aid issued by Teva and Aventis Pharma (now Sanofi-Aventis). Copaxone was indicated for the treatment of patients with relapsing remitting multiple sclerosis (MS) as was Schering Health Care's product Betaferon (interferon beta-lb (IFNB-1b)).

A page of the detail aid entitled 'Patients choose to stay with Copaxone', featured three pie charts to illustrate the claim 'Glatiramer acetate [Copaxone] has the most favourable adverse effect profile of all agents available to treat MS'. The relevant pie chart for Betaferon showed that only 4% of patients recruited for the IFNB-1b trial remained on treatment after 5 years. Schering Health Care stated that this figure was inaccurate. More importantly, the pie chart was presented in such a way as to suggest that all but 4% of patients recruited to Betaferon's pivotal study withdrew prematurely as a consequence of adverse events or poor compliance.

Schering Health Care explained that only 1.3% of patients recruited, not 4%, completed at least 5 years of study treatment (either IFNB-1b or placebo). This was because the study was terminated when all patients had reached 3 years of follow up, due to the positive outcome in the highest dose IFNB-1b group (now the licensed dose) versus placebo. Recruitment had taken place gradually over 2 years and so by the time all patients had completed 3 years' follow up, only 5 of the earliest-recruited patients had completed 5 years of treatment.

Schering Health Care alleged that it was therefore extremely misleading to imply that the low patient numbers completing 5 years in the Betaferon pivotal study was the result of premature withdrawal due to adverse reactions, poor compliance or any other reason. Schering Health Care alleged that the implication that Betaferon had poor long-term tolerability was a breach of the Code.

Schering Health Care further alleged that it was inappropriate and misleading to unfavourably compare numbers of patients in the Betaferon pivotal trial who (by accident of their recruitment date) happened to have 5 years of data available in a placebo-controlled study terminated at 3 years, to numbers of patients continuing treatment as part of prospective, open-label extension studies for other products (as in the other two pie charts on the same page).

Finally, the presentation of data in the detail aid appeared to have been deliberately manipulated so as to put Betaferon in the worst possible light compared with Copaxone. Betaferon, like Copaxone, was intended to be taken long-term for control of a lifelong disease. It would be a very serious matter if such a product managed to retain only 4% of patients on treatment over a planned 5 year follow up period, for whatever reason. The detail aid was factually inaccurate and it falsely implied that this was exactly what happened in the Betaferon pivotal study. This implication was potentially very damaging to Betaferon, and amounted to a seriously disparaging reference in breach of the Code.

The Panel noted that the page of the detail aid at issue was headed 'Patients choose to stay with Copaxone'. A sub-heading read 'Glatiramer acetate [Copaxone] has the most favourable adverse effect profile of all agents available to treat MS'. Immediately below the subheading was a highlighted box showing the 'Proportion of patients remaining in pivotal studies'. Three pie charts showed that more than 60% of Copaxone patients originally recruited remained on treatment within a study after 10 years, only 48% of IFNB-1a patients completed a dose blinded study after 6 years and only 4% of patients recruited for the IFNB-1b trial remained on treatment after 5 years respectively.

The Panel noted that the heading and sub-heading appeared to relate to the general clinical situation and not just that found in clinical trials. Although the pie charts related to clinical trials the data had been set in the context of general treatment; the Panel therefore considered that it was not unreasonable that it would be regarded as such by some readers. The 4% figure quoted for IFNB-1b was not an accurate reflection of the study at issue. A minority of patients had remained on treatment for a full five years because the trial had a two year recruitment period and was stopped after 3 years. The Panel noted Schering Health Care's submission that over 5 years only 21 patients (5.6%) withdrew because of adverse events.

The Panel considered that within the context of the page the pie chart implied that, within 5 years, 96% of patients treated with IFNB-1b would discontinue therapy because of adverse effects. This was not so. The comparison shown was unfair and inaccurate as alleged. Breaches of the Code were ruled. The Panel considered that Betaferon had been disparaged. A breach of the Code was ruled.

Schering Health Care Ltd complained about a Copaxone (glatiramer acetate) detail aid (ref CO704/229) issued by Teva Pharmaceuticals Ltd and Aventis Pharma Ltd (now Sanofi-Aventis). Copaxone was indicated for the reduction in frequency of relapses in ambulatory patients with relapsing remitting multiple sclerosis (MS) characterised by at least two attacks of neurological dysfunction over the preceding two year period. Schering Health Care marketed Betaferon (interferon beta-lb (IFNB-1b)) which was indicated for the treatment of patients with relapsing remitting MS and two or more relapses within the last two years. Betaferon was also indicated for patients with secondary progressive MS with active disease, evidenced by relapses.

Intercompany correspondence had failed to resolve the issue.

COMPLAINT

Schering Health Care alleged that the detail aid presented data from the pivotal study of Betaferon in such a way as to mislead the reader and to disparage, by implication, the safety and tolerability of Betaferon compared with Copaxone. Teva stated that the detail aid had been withdrawn as part of the normal marketing cycle, but did not accept that it was either inaccurate or misleading and did not give any undertaking not to repeat the claim in future.

Page 8 of the detail aid (entitled 'Patients choose to stay with Copaxone'), featured three pie charts to illustrate the claim 'Glatiramer acetate [Copaxone] has the most favourable adverse effect profile of all agents available to treat MS'. The relevant pie chart for Betaferon stated that only 4% of patients recruited for the IFNB-1b trial remained on treatment after 5 years. Schering Health Care alleged that the figure of 4% was inaccurate. More importantly, the pie chart and its legend were presented in such a way as to suggest that all but 4% of patients recruited to Betaferon's pivotal study withdrew prematurely as a consequence of adverse events or poor compliance.

Teva referenced the IFNB-1b pie chart to the IFNB Study Group (1995) which stated that 5 patients (ie 1.3% of the 372 patients recruited, not 4%) completed at least 5 years of study treatment (either IFNB-1b or placebo). However, the paper also clearly stated that the study was terminated by the external advisory board when all patients had reached 3 years of follow up. This was because of the positive outcome in the highest dose IFNB-1b group (now the licensed dose) versus placebo. It was not intended for all patients on study to have 5 years of follow up. Because patient recruitment took place gradually over 2 years, by the time all patients had completed 3 years' follow up, a proportion of patients had completed between 3 and 5 years of follow up. 166 patients (44.6% of the total) had annualised relapse rate data to year 5 by the time the 3-year study reached completion. A very small number (5) of the earliest-recruited patients had even completed 5 years of treatment by the time the study was terminated at 3 years. Schering Health Care noted that withdrawals from the study, with timing and reasons, were listed in full in the paper. The most common reason for withdrawal was failure to consent for an extension of study follow up beyond the original 2 and 3-year protocols, and in many cases these patients would have continued on compassionate IFNB-1b treatment outside the study. Over 5 years, only 21 patients (5.6%) withdrew from the study treatment (including placebo) because of adverse events.

It was therefore extremely misleading to imply that the low patient numbers completing 5 years in the Betaferon pivotal study was the result of premature withdrawal due to adverse reactions, poor compliance or any other reason. The number of patients at 5 years was actually an artefact of having a 2-year recruitment period for a 3-year data collection period. Schering Health Care alleged that the implication that Betaferon had poor long-term tolerability was a breach of Clause 7.2 of the Code.

Schering Health Care further alleged that it was inappropriate and misleading to unfavourably compare numbers of patients in the Betaferon pivotal trial who (by accident of their recruitment date) happened to have 5 years of data available in a placebo-controlled study terminated at 3 years, to numbers of patients continuing treatment as part of prospective, open-label extension studies for other products (as in the other two pie charts on the same page). Schering Health Care alleged that this comparison was unfair and inaccurate in breach of Clause 7.3 of the Code.

Finally, the presentation of data in the detail aid appeared to have been deliberately manipulated so as to put Betaferon in the worst possible light compared with Copaxone. Betaferon, like Copaxone, was intended to be taken long-term for control of a lifelong disease. It would be a very serious matter if such a product managed to retain only 4% of patients on treatment over a planned 5 year follow up period, for whatever reason. The Copaxone detail aid was not only factually inaccurate, but it falsely implied that this was exactly what happened in the Betaferon pivotal study. Schering Health Care stated that this implication was potentially very damaging to Betaferon, and amounted to a seriously disparaging reference in breach of Clause 8.1 of the Code.

RESPONSE

Teva submitted a joint response on behalf of both companies.

Teva disagreed with Schering Health Care's interpretation of page 8 of the detail aid. The page, entitled 'Patients choose to stay with Copaxone', gave five examples of this in the clinic; lack of need for blood testing, low excess of depression on therapy, better compliance with therapy, most favourable adverse event profile and proportion of patients staying in long-term follow up in pivotal clinical studies. As the page was clearly about a range of factors influencing and illustrating patients' decisions to stay on Copaxone, Teva disagreed with Schering Health Care's assertion that the pie chart implied that all patients withdrew from their pivotal studies because of adverse events. There were no reasons stated for patients leaving the pivotal studies for any of the products compared in the pie charts. Neurologists would know that patients left studies for a variety of reasons.

The referenced paper stated that only five patients recruited into this pivotal study completed year 5. As noted by Schering Health Care the 'most common reason for withdrawal was failure to consent for an extension of study follow up'. This was exactly in keeping with Teva's interpretation of the pie chart; for a range of reasons patients chose not to carry on with follow up studies for IFNB-1b, in direct contrast to the patients in the Copaxone pivotal study follow up. The title on the graphic was explicit that it referred only to 'proportion of patients remaining in pivotal studies'. This graphic was no more linked to the quote above it, regarding the favourable adverse event profile, than it was to the bullet point below, regarding the lack of need for liver function or blood tests with Copaxone use. It simply illustrated relative proportions of patients choosing to continue with formal study follow up.

PANEL RULING

The Panel noted that the page of the detail aid at issue was headed 'Patients choose to stay with Copaxone'. A sub-heading read 'Glatiramer acetate [Copaxone] has the most favourable adverse effect profile of all agents available to treat MS'. Immediately below the subheading was a highlighted box showing the 'Proportion of patients remaining in pivotal studies'. Three pie charts showed that more than 60% of Copaxone patients originally recruited remained on treatment within a study after 10 years, only 48% of IFNB-1a patients completed a dose blinded study after 6 years and only 4% of patients recruited for the IFNB-1b trial remained on treatment after 5 years respectively.

The Panel noted that the heading and sub-heading appeared to relate to the general clinical situation and not just that found in clinical trials. Although the pie charts related to clinical trials the data had been set in the context of general treatment; the Panel therefore considered that it was not unreasonable that it would be regarded as such by some readers. The 4% figure quoted for IFNB-1b was not an accurate reflection of the study at issue. A minority of patients had remained on treatment for a full five years because the trial had a two year recruitment period and was stopped after 3 years. The Panel noted Schering Health Care's submission that over 5 years only 21 patients (5.6%) withdrew because of adverse events.

The Panel considered that within the context of the page the pie chart implied that, within 5 years, 96% of patients treated with IFNB-1b would discontinue therapy because of adverse effects. This was not so. The comparison shown was unfair and inaccurate as alleged. Breaches of Clauses 7.2 and 7.3 were ruled. The Panel considered that Betaferon had been disparaged. A breach of Clause 8.1 was ruled.

Complaint received	**4 March 2005**
Cases completed:	
Case AUTH/1687/3/05	**12 May 2005**
Case AUTH/1699/3/05	**16 May 2005**

CASE AUTH/1688/3/05

GENERAL PRACTITIONER v ASTRAZENECA

Invitation to meeting for nurses

A general practitioner complained about an invitation to nurses to attend a meeting hosted by AstraZeneca. The invitation showed that the evening would consist of one hour's education followed by dinner. The complainant alleged that the meeting breached the Code in that the hospitality was excessive for one hour of education and was the primary inducement for attendance.

The Panel noted that the complainant appeared not to have attended the meeting; the complaint had been made on the basis of the invitation sent by AstraZeneca. The invitation stated that the meeting would begin at 7.15pm; a presentation 'Asthma/COPD and the GMS Contract' would begin at 7.30pm and discussion and questions would follow at 8.15pm and dinner would be served at 8.30pm.

The agenda for the actual meeting was different in that an additional 45 minute presentation by a practice nurse was added and dinner was not served until 9pm. The updated agenda was given to the nurses when they arrived for the meeting. Dinner consisted of a two-course set meal plus drinks at a cost of £27.80 per head.

The Panel noted AstraZeneca's submission that it was common practice to change meeting agendas after invitations had been issued. Nonetheless the company had issued invitations to a meeting which had shown that there would only be one hour of educational content; the full programme had not been disclosed and so it was thus possible that some attendees at least had accepted the invitation on the basis of the hospitality offered. The Panel considered that although details of meeting agendas could be changed nearer the time the addition of a 45 minute presentation went beyond fine tuning timings or adding speakers' names and titles as submitted by AstraZeneca.

The Panel considered that the arrangements for the meeting as described on the invitation were unacceptable. The educational content was not sufficient to justify the hospitality. In relation to the invitation high standards had not been maintained. Breaches of the Code were ruled.

The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure. The Panel did not consider that the invitation was such as to warrant a ruling of breach of Clause 2.

A general practitioner complained about an invitation to a meeting to be held by AstraZeneca UK Limited. The copy of the invitation provided by the complainant showed that the meeting, entitled 'Asthma/COPD [Chronic obstructive pulmonary disease] and the GMS [General Medical Services] Contract', commenced at 7.15pm. The speaker's presentation started at 7.30pm; at 8.15pm there was a discussion and questions and dinner followed at 8.30pm.

COMPLAINT

The complainant alleged that the meeting breached the Code in that the hospitality was excessive for one hour of education and was the primary inducement for attendance. He noted that it was directed at nurses.

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

The meeting was also referred to in an article in The Sunday Times, 27 February 2005 which had been taken up as a separate complaint (Case AUTH/1683/2/05).

RESPONSE

AstraZeneca stated that the meeting was an educational evening for practice nurses who specialised in running asthma and COPD clinics. The agenda focused on the new GMS contract within primary care relating to management of COPD and asthma. The GMS contract relating to respiratory disease was a topical area for asthma specialised practice nurses. The invitees were chosen by the local sales team based on their specific interest in COPD and asthma.

The main speaker was to provide a 45 minute educational presentation on details of the GMS contract relating to managing chronic respiratory disorders, COPD and asthma within primary care. A further speaker, a practice nurse, was later added to the agenda following her confirmation after the initial preliminary invitation had been sent out. She was to provide further information on how the GMS contract related specifically to the asthma clinic nurse and discuss particular case studies with the meeting attendees. The updated agenda was given out to the seventeen nurses when they arrived at the meeting.

It was common meeting practice that further details on exact timings and speakers' names and titles were added to an agenda after an invitation had been sent out. This was to give invitees sufficient time to consider their attendance as well as to allow speakers to confirm their attendance.

The meeting and the dinner were held in a private room. The total presentation and discussion period lasted two hours which AstraZeneca considered appropriate in terms of educational content for an evening meeting. The two course set dinner cost £19 per head and the total bill for those who ate was £417 (£27.80 per head) which included all drinks. AstraZeneca submitted that this represented good value for the meal served and was no more than attendees would be expected to pay themselves.

AstraZeneca therefore denied that this meeting was in breach of Clauses 2, 9.1 and 19.1 of the Code.

PANEL RULING

The Panel noted AstraZeneca's submission that the meeting in question was for asthma/COPD nurses. The letter of invitation provided by the complainant, however, began 'Dear Doctor' to which someone had added, in handwriting '/Nurse'. The letter had been signed by an AstraZeneca representative and it appeared that she had added to the bottom of the letter 'Give me a call and let me know if you can make it. Also any GPs that want to attend. Thanks'. It further appeared that the complainant, a GP, had not attended the meeting; the complaint had been made on the basis of the invitation sent by AstraZeneca. The invitation stated that the meeting would begin at 7.15pm and at 7.30pm the speaker would deliver a presentation entitled 'Asthma/COPD and the GMS Contract'. Discussion and questions would follow at 8.15pm and dinner would be served at 8.30pm. There was no mention that a second speaker would be present thus extending the educational content of the meeting until 9pm.

The agenda for the actual meeting was different in that after the first speaker an additional 45 minute presentation by a practice nurse was added and dinner was to be at 9pm. The additional presentation provided further information on how the GMS contract related specifically to the asthma clinic nurse and particular case studies. The updated agenda was given to 17 asthma nurses when they arrived for the meeting.

The meeting was followed by a two-course set meal plus drinks at a cost per head of £27.80.

The Panel noted that from the original agenda the planned educational content was an hour followed by dinner in a private room. The agenda for the actual meeting had been extended by 30 minutes. It was not known what time the meeting finished. The bill gave the time as 10.22pm.

The Panel noted AstraZeneca's submission that it was common practice that further details on exact timings and speakers' names and titles were added to an agenda after an invitation had been sent out. The Panel noted, however, that the supplementary information to Clause 19.1 stated that with any meeting, it should be the programme that attracted delegates and not the associated hospitality or venue. AstraZeneca had issued invitations to a meeting which had shown that there would only be one hour of educational content; the full programme had not been disclosed in the agenda and so it was thus possible that some attendees at least had accepted the invitation on the basis of the hospitality offered. The Panel considered that although details of meeting agendas could be changed nearer the time the addition of a 45 minute presentation went beyond fine tuning timings or adding speakers' names and titles as submitted by AstraZeneca.

The Panel noted that the complaint concerned the invitation. The arrangements for the meeting as described on the invitation were unacceptable. The educational content was not sufficient to justify the hospitality. A breach of Clause 19.1 was ruled. The Panel considered that in relation to the invitation high standards had not been maintained and ruled a breach of Clause 9.1.

The Panel noted that Clause 2 of the Code stated that, *inter alia*, activities associated with promotion must never be such as to bring discredit upon, or reduce confidence in, the pharmaceutical industry. A ruling of a breach of Clause 2 was a sign of particular censure and was reserved for such circumstances. The Panel did not consider that the invitation was such as to warrant a ruling of breach of this clause and so no breach of Clause 2 was ruled.

Complaint received **3 March 2005**

Case completed **28 April 2005**

CASE AUTH/1690/3/05

PRIMARY CARE TRUST MEDICINES MANAGEMENT AND PRESCRIBING LEAD v GLAXOSMITHKLINE

Provision of service

The medicines management and prescribing lead to a primary care trust (PCT) complained about an Airways Integrated Management Service (AIMS) conducted at a practice within the PCT by GlaxoSmithKline. The complainant alleged that high standards had not been maintained as signatures were not obtained to allow the review to go ahead or to authorize changes to patients' medication and records. In addition the nurse advisor did not appear to follow a protocol. The practice had told GlaxoSmithKline that it no longer wished to continue with the service. The company's actions had caused the practice and the PCT to lose confidence in the pharmaceutical industry.

The Panel was extremely concerned about arrangements at the practice in question; the implementation of the AIMS programme was contrary to the protocol and GlaxoSmithKline procedures. Signed consent for the review to go ahead was not obtained nor was signed consent obtained for the alteration of patients' medication. Both representatives and a nurse adviser were involved which was contrary to the protocol.

The Panel considered that the implementation of the AIMS programme at the practice was totally unacceptable. The Panel considered that the failure to follow the protocol was in breach of the Code. High standards had not been maintained. Breaches of the Code were ruled.

The Panel noted that Clause 2 of the Code was reserved as a mark of particular censure. The Panel considered that the circumstances warranted a ruling of a breach of Clause 2 of the Code and ruled accordingly.

The medicines management and prescribing lead, to a primary care trust (PCT), complained about an Airways Integrated Management Service (AIMS) conducted at a practice within the PCT by GlaxoSmithKline UK Limited.

COMPLAINT

The complainant alleged that following feedback from a practice manager and a prescribing support pharmacist about the implementation of AIMS within their practice, Clauses 2 and 9.1 of the Code had been breached.

High standards were not maintained as GlaxoSmithKline did not obtain signed consent for the review to go ahead, the nurse adviser did not obtain signed consent to authorize her to alter patients' medication and records. In addition the nurse adviser did not appear to follow a protocol, for example no audit trail was left in patients' records after altering medication or sending letters. Patients who had medication altered but did not come in for review were not followed up. The few patients who were seen were not offered follow-up and chronic obstructive pulmonary disease (COPD) patients were not reviewed any differently to asthma patients.

The practice manager and prescribing support pharmacist had discussed the matter with representatives from GlaxoSmithKline and the practice has subsequently informed the company that it no longer wished to continue with the service. The company's actions had caused the practice and the PCT to lose confidence in the pharmaceutical industry.

GlaxoSmithKline was asked to respond to Clause 18.1 as well as Clauses 2 and 9.1 cited by the complainant.

RESPONSE

GlaxoSmithKline accepted that the way the AIMS programme was implemented at the practice in question was contrary to both the AIMS protocol and GlaxoSmithKline procedures, and as such the company accepted a breach of Clauses 9.1 and 18.1. GlaxoSmithKline did not consider that there was a breach of Clause 2.

A number of GlaxoSmithKline members of staff and a third party nurse were involved in this project. The GlaxoSmithKline staff were immediately suspended and dealt with via internal disciplinary procedures. The nurse was no longer engaged by GlaxoSmithKline, nor would she be in the future.

GlaxoSmithKline provided copies of AIMS materials as they should be correctly implemented within a programme but its investigations led it to believe that at the surgery in question the nurse did not use any printed material.

AIMS at the surgery in question

The internal investigation revealed that:

- GlaxoSmithKline staff acted outside the Code, outside GlaxoSmithKline's operational guidelines, protocols for implementation of AIMS and in contravention of internal guidance.
- As a consequence, a therapy review proceeded without signed consent from the practice. High standards were not maintained and therefore GlaxoSmithKline accepted a breach of Clause 9.1 occurred.
- In direct contravention of internal guidance, promotional representatives became involved with the delivery of a medical service. The GlaxoSmithKline staff concerned did not follow the protocol for AIMS implementation and, in addition, the nurse involved did not adhere to agreed patient review protocols and GlaxoSmithKline therefore accepted a breach of Clause 18.1.

Whilst accepting that the implementation of AIMS at the surgery did not maintain high standards, the intention, approved protocols and usual service supported by GlaxoSmithKline were carefully proscribed. The service had a rigorous protocol which had been satisfactorily used by many practices.

AIMS was a service designed to assist doctors review asthmatics currently treated with both an inhaled corticosteroid (ICS) and an inhaled long acting bronchodilator (LABA). After the review by the doctor, patients could be switched to a therapeutically equivalent combination therapy if appropriate.

AIMS implementation process flow

The AIMS programme, which evolved from a CFC transition service, was designed to assist doctors review patients receiving both ICS and LABA to a therapeutically equivalent combination, if appropriate. The potential benefits for both the patients and the practice were:

- Simplified treatment using a single inhaler
- Improved control and compliance
- Cost savings: based on national GP database information, for an average GP practice of 4,500 patients, the potential cost saving could be over £5,500 per year. Patients paid one prescription charge and the NHS paid one dispensing fee
- CFC transition

Process

Normally the AIMS programme was promoted but not delivered by a team of 60 dedicated AIMS representatives. They were a promotional sales force and had completed both internal GlaxoSmithKline training and had passed the ABPI examination.

Doctors were introduced to the concept of AIMS either via the AIMS representative, who called in person to make an appointment or via a letter of introduction outlining the AIMS programme.

Overview of the normal AIMS programme process.

- The practice decided which patient types it wished to review and authorized this decision.
- Either a specialist independent IT company or practice staff (nurse, doctor, pharmacists or manager) searched the practice computer for patients fulfilling selection criteria and produced a list. This process was authorized by the doctors. The AIMS protocols did not allow a third party nurse to be involved in this process and internal GlaxoSmithKline guidance forbade the recommendation of specific third party nurses.
- The doctors reviewed the list and decided upon an appropriate course of action eg a therapy change or an invitation to attend for an asthma review. This activity was solely agreed and authorized by the doctors. Patient information remained confidential and was retained within the practice.
- The prescribing database was upgraded by an agency or practice staff.
- Patients for whom a therapy change was made without asthma review were sent a letter of notification, customized by the practice, along with a patient feedback card.
- If agency staff were not required, remuneration of £15 per hour, up to a maximum of 15 hours, was available to support the practice in this review process. Practices were under no obligation to avail themselves of this offer of remuneration.

Implementation

If the practice decided to proceed with the AIMS programme, it might do so, either by using agency staff or practice staff.

Via an agency

- An AIMS authorization form was used.
- Sections A, B, C and D of the form were completed at the time of the agreement to the service. At this point the GP authorized the file search to identify patients who might be suitable for a therapy transfer. The choice of patients and search criteria used were entirely the doctor's decision. This search required two signatories, both of whom must be GPs. A written undertaking to ensure transparency of communication with the practice was required. Written authorization by two signatories to conduct a computer search of patients currently prescribed an inhaled LABA together with an ICS via metered dose or dry powder inhalers was required, and both signatories must be GPs. The facilitator from the agency must give a written undertaking of confidentiality. A medication list for the file search was determined, which also required written authorization by a GP.
- The GP reviewed the list of patients generated by the file search, and identified those whom he wished to review in person. The GP authorized the facilitator from the agency to make the repeat medication changes to the database. This review and authorization was confirmed in writing in Section E by the GP.
- Patients were informed of the planned change or invited to make an appointment for an asthma review via a letter from the practice. Sample letters were provided in the Patient Sample Letter pack, which might be customized by the practice as appropriate. A patient feedback card was included with those letters notifying a planned transfer of therapy.
- Final sign off for completion of the AIMS programme (Section F) was given only when the practice was satisfied that all stages of the review process had been carried out in accordance with the agreed procedures.
- Once completed the authorization form was returned to the agency by the agency facilitator.

Via practice staff

- An AIMS Application for Financial Support form was used, if the practice desired remuneration for practice time.
- Sections A, B, C and D of the form were

completed at the time of agreement to initiate review.

- The GP reviewed the list of patients generated by the file search, identified those whom he wished to review in person and nominated a member of practice staff to complete repeat medication changes on the prescription database, according to written instructions in section E of the AIMS Authorization Form.
- Patients were informed of the planned treatment change or invited to make an appointment for asthma review via a letter from the practice. Sample letters were provided in the Patient Sample Letter pack, which might be customized by the practice as appropriate. A patient feedback card was included with those letters notifying a planned transfer of therapy.
- Final sign off for completion of the AIMS programme (Section F) was given only when the practice was satisfied that all stages of the review process had been carried out in accordance with the agreed procedures. If the practice completed an application for funding this was sent to or collected by the representative and the application was processed by GlaxoSmithKline.

As outlined above, when initiated according to protocol GlaxoSmithKline considered the AIMS programme was intended to deliver potential benefits to the patient, practice and NHS and was fully compliant with the requirements of Clause 18.1 of the Code.

On hearing of this complaint GlaxoSmithKline acted rapidly to suspend those involved pending investigation prior to taking appropriate disciplinary action. While there was no doubt that GlaxoSmithKline protocols were not adhered to, and signed consent was not obtained, the representatives involved believed they were proceeding with the full consent of one of the doctors at the surgery who, although in receipt of appropriate paperwork, had not completed the paperwork as expected. GlaxoSmithKline accepted that this did not excuse the actions of the individuals.

As a direct result of this case, there would be widespread internal publicizing of this incident – and the serious disciplinary actions that have resulted from it – and retraining for all individuals involved in AIMS to prevent similar incidents occurring.

GlaxoSmithKline submitted that the issue at the surgery in question was an isolated case and was not representative of the majority of AIMS projects and individuals who followed the proscribed protocol. The overarching theme to the AIMS programme was about potential benefit to patients, practices and the NHS, and as such GlaxoSmithKline should not therefore be found in breach of Clause 2.

Summary

- After internal investigation GlaxoSmithKline accepted that breaches of Clauses 9.1 and 18.1 occurred during the implementation of the AIMS programme at the surgery.
- The AIMS protocols and supporting guidance were robust and complied with Clause 18.1, and the intention of the AIMS programme was to deliver potential benefit to practice, patient and the NHS.
- The breaches occurred as an isolated incident where GlaxoSmithKline staff did not adhere to internal guidance nor to agreed AIMS protocols.
- The GlaxoSmithKline staff involved had been dealt with through disciplinary procedures, and the nurse involved now had no association with GlaxoSmithKline.
- GlaxoSmithKline had taken this matter extremely seriously and had reviewed and started to implement further training for all AIMS representatives and their managers.
- Since the protocols and intentions were ethical and within the Code and since the events were due to exceptional behaviour of a small number of representatives GlaxoSmithKline did not consider that it was in breach of Clause 2.

PANEL RULING

The Panel noted that the complaint concerned the implementation of AIMS at the practice in question. There was no allegation about the general acceptability of AIMS in relation to the requirements of Clause 18.1.

The Panel was extremely concerned about arrangements at the practice in question; the implementation of the AIMS programme was contrary to the protocol and GlaxoSmithKline procedures. Signed consent for the review to go ahead was not obtained nor was signed consent obtained for the alteration of patients' medication. Neither the complainant nor GlaxoSmithKline gave any details about what changes had been made to patients' medication. Both representatives and a nurse adviser were involved which was contrary to the protocol.

The Panel considered that the implementation of the AIMS programme at the practice was totally unacceptable. The Panel considered that the failure to follow the protocol was in breach of Clause 18.1 of the Code and ruled accordingly. High standards had not been maintained and thus a breach of Clause 9.1 of the Code was ruled.

The Panel noted that Clause 2 of the Code was reserved as a mark of particular censure. The Panel considered that the circumstances warranted a ruling of a breach of Clause 2 of the Code and ruled accordingly.

Complaint received **11 March 2005**

Case completed **2 June 2005**

CASE AUTH/1691/3/05

SHIRE v STRAKAN

Promotion of Adcal-D_3

Shire complained about an Adcal-D_3 (calcium and vitamin D_3) leavepiece and journal advertisement, issued by Strakan, both of which compared the cost of Adcal-D_3 with that of Calcichew-D_3. Shire marketed Calcichew-D_3 and Calcichew-D_3 Forte.

Shire noted that the promotional items correctly stated that the price of Adcal-D_3 was less than half the price of Calcichew-D_3. However, in Shire's view the price of Adcal-D_3 should be compared with that of Calcichew-D_3 Forte, which was closely equivalent in dose and had a very similar price. Vitamin D content was especially important. Since this price comparison was not made on the basis of the equivalent dosage requirement for the same indications, Shire alleged that like was not compared with like and the comparison was unfair and misleading.

The Panel noted that both the leavepiece and the advertisement referred to the 'evidence-based ratio' of calcium and vitamin D_3 used in Chapuy *et al* (1992). Chapuy *et al* had used a daily calcium to vitamin D_3 ratio of 1.2g: 800IU. Thus given the context in which the cost comparison appeared the Panel considered that this ratio should be its basis. Although neither Calcichew-D_3 Forte nor Calcichew-D_3 provided an identical calcium:vitamin D_3 ratio to that provided by Adcal-D_3, in the Panel's view the ratio provided by Calcichew-D_3 Forte (1g:800IU) was a closer match to Adcal-D_3 (1.2g:800IU) than that provided by Calcichew-D_3 (1g:400IU (bd) or 1.5g:600IU (tds)).

The Panel considered that given the basis of the cost comparison as stated in the advertisement (evidence-based ratio) and the leavepiece (evidence-based ratio and one tablet bd dosage) it was unfair and misleading to compare the cost of Adcal-D_3 with that of Calcichew-D_3 as alleged. Whilst the comparison was presented in a clinical context the actual comparison related to cost alone. This was not made sufficiently clear and was unacceptable. Breaches of the Code were ruled.

Shire Pharmaceuticals Ltd complained about the promotion of Adcal-D_3 (calcium carbonate and vitamin D_3) by Strakan Pharmaceuticals Limited. The items at issue were a leavepiece (ref M001/156) and a journal advertisement (ref M001/0157). Correspondence between the parties had failed to resolve the matter. Shire supplied Calcichew-D_3 and Calcichew-D_3 Forte.

The leavepiece was for general practitioners and hospital doctors. The relevant section stated:

'Just Adcal-D_3

– Provides an evidence-based ratio

– A one tablet b.d. dosage

– All this and less than half the price of Calcichew-D_3

Adcal D_3 costs £7.25 for 100 tablets'

The journal advertisement stated:

'Adcal-D_3 is the only tablet that allows you to deliver the evidence-based ratio of calcium and vitamin D_3 used in the landmark Chapuy trial. It's also only half the cost of Calcichew-D_3'.

COMPLAINT

Shire noted that the promotional items correctly stated that the price (or cost) of Adcal-D_3 was less than half the price of Calcichew-D_3. However, in Shire's view the price of Adcal-D_3 should be compared with that of Calcichew-D_3 Forte, which was closely equivalent in dose and had a very similar price. The maximum licensed daily dose (twice daily) for Adcal-D_3 was 1.2g calcium and 800IU vitamin D. The corresponding maximum daily dose (three times daily) for Calcichew-D_3 was 1.5g calcium and 600IU vitamin D and for Calcichew-D_3 Forte (twice daily) was 1g calcium and 800IU vitamin D. Vitamin D content was especially important.

Since this price comparison was not made on the basis of the equivalent dosage requirement for the same indications, Shire alleged that like was not compared with like and the comparison was unfair and misleading in breach of Clauses 7.2 and 7.3 of the Code.

Shire noted that Calcichew-D_3 Forte was the most widely used product with 2004 pack sales (100 tabs) of 1,315,000 compared with Calcichew-D_3 with pack sales (100 tabs) of 532,000 (data: IMS BPI Mat Dec 2004).

RESPONSE

Strakan entirely refuted the assertion that the leavepiece and the advertisement were in breach of Clauses 7.2 and 7.3 of the Code. There were several branded and generic calcium/vitamin D supplements available in the UK which were marketed and prescribed as part of management strategies for the prevention and treatment of osteoporosis. Strakan listed each product showing the daily amounts of calcium and vitamin D which were delivered by their maximum recommended daily dose.

The licensed indications for Calcichew-D_3 and Adcal-D_3, as listed in their respective summaries of product characteristics (SPCs) were:

Calcichew-D_3

'Calcichew D_3 chewable tablets should be used only as a therapeutic and not as a food supplement when the diet is deficient or when normal requirements of both components is increased.

Calcichew D_3 chewable tablets may be used as an adjunct to specific therapy of osteoporosis or as a therapeutic supplement in established osteomalacia, pregnant patients at high risk of needing such a therapeutic supplementation or malnutrition when dietary intake is less than that required.'

Adcal-D_3

'As an adjunct to specific therapy for osteoporosis and in situations requiring therapeutic supplementation of malnutrition eg in pregnancy and established vitamin D dependent osteomalacia.

The prevention and treatment of calcium deficiency/vitamin D deficiency especially in the housebound and institutionalised elderly subjects. Deficiency of the active moieties is indicated by raised levels of PTH, lowered 25-hydroxy vitamin D and raised alkaline phosphatase levels which are associated with increased bone loss.'

There was variation in the daily doses of both calcium and vitamin D delivered by all of the products with very similar indications reflecting the lack of clinical consensus as to the precise dose of calcium and vitamin D required for supplementation in these circumstances. The dose of calcium delivered by Adcal-D_3 was slightly more than that delivered by Calcichew-D_3 Forte and the dose of vitamin D and calcium delivered by Adcal-D_3 was slightly more than that delivered by Calcichew-D_3.

The decision to compare with Calcichew-D_3 rather than Calcichew-D_3 Forte, or indeed any of the other products, was a commercial one. In the market for dietary supplementation and adjunctive therapy for osteoporosis it was clear that on the basis of market share Calcichew-D_3 (26.3%) was Strakan's nearest competitor and not Calcichew-D_3 Forte (40.7%) (Adcal-D_3 had a 23.8% market share; four other products shared the remaining 9% of the market). Given that the licensed indications for Adcal-D_3 and Calcichew-D_3 were essentially identical and that there was no suggestion that clinicians prescribed Calcichew-D_3 for different groups of patients compared with the other products, it seemed clear to Strakan that there was an opportunity to point out to clinicians that its product was much less expensive that Calcichew-D_3 and that much needed NHS resources could be saved. Indeed, the price comparison made was extremely conservative, based only on a twice a day dosage of Calcichew-D_3. If Strakan had used the maximum daily dose (required to deliver 600IU of vitamin D) it could have shown that Calcichew-D_3 was three times as expensive as Adcal-D_3.

In summary, Calcichew-D_3, like Adcal-D_3, was licensed as a dietary supplementation and as an adjunctive therapy for osteoporosis. It was used in exactly the same group of patients as Adcal-D_3 and was Adcal-D_3's closest competitor in terms of market share. There was no clinical consensus as to the precise dose of calcium and vitamin D required to manage these conditions and this was reflected in the variety of formulations available. Hence, Strakan submitted that it was within its rights to compare the price of Adcal-D_3 with that of Calcichew-D_3 and that no breaches of Clauses 7.2 and 7.3 had occurred or were intended.

PANEL RULING

The Panel noted that both the leavepiece and the advertisement referred to the 'evidence-based ratio' of calcium and vitamin D_3 used in Chapuy *et al* (1992). Chapuy *et al* had used a daily calcium to vitamin D_3 ratio of 1.2g: 800IU. Thus given the context in which the cost comparison appeared the Panel considered that this ratio should be its basis. In that regard the Panel noted that Adcal-D_3 provided a daily calcium:vitamin D_3 ratio of 1.2g:800IU, Calcichew-D_3 Forte provided a daily ratio of 1g:800IU, twice daily Calcichew-D_3 provided a daily ratio of 1g:400IU and if Calcichew-D_3 was taken three times daily the daily calcium:vitamin D_3 ratio was 1.5g:600IU. Although neither Calcichew-D_3 Forte nor Calcichew-D_3 provided an identical calcium:vitamin D_3 ratio to that provided by Adcal-D_3, in the Panel's view the ratio provided by Calcichew-D_3 Forte (1g:800IU) was a closer match to Adcal-D_3 (1.2g:800IU) than that provided by Calcichew-D_3 (1g:400IU or 1.5g:600IU).

The Panel considered that given the basis of the cost comparison as stated in the advertisement (evidence-based ratio) and the leavepiece (evidence-based ratio and one tablet bd dosage) it was unfair and misleading to compare the cost of Adcal-D_3 with that of Calcichew-D_3 as alleged.

Whilst the comparison was presented in a clinical context the actual comparison related to cost alone. This was not made sufficiently clear and was unacceptable. Breaches of Clauses 7.2 and 7.3 were ruled.

Complaint received **14 March 2005**

Case completed **29 April 2005**

CASES AUTH/1693/3/05 and AUTH/1694/3/05

LUNDBECK v LILLY and BOEHRINGER INGELHEIM

Promotion of Cymbalta

Lundbeck complained about a Cymbalta (duloxetine) detail aid and a dosing guide issued by Lilly and Boehringer Ingelheim. Cymbalta was a combined serotonin and noradrenaline reuptake inhibitor (SNRI) for the treatment of major depressive episodes. Lundbeck supplied Cipramil and Cipralex, selective serotonin reuptake inhibitors (SSRIs) indicated, *inter alia*, for the treatment of depression.

The claim 'An option for depressed patients failing to respond to an SSRI, was supported by the explanation 'current guidelines for the treatment of depression state that if a patient fails to achieve remission on an antidepressant, they should be switched to another class of drug.' The explanation was referenced in the small print to The Maudsley 2003 Prescribing Guidelines. Lundbeck alleged that the phrase 'current guidelines' misled as clinicians might assume the guidelines in question were those issued by the National Institute for Clinical Excellence published in December 2004 and not the Maudsley guidelines as referenced. Lundbeck further alleged that whichever guidelines were considered, neither of them specifically recommended that patients who had failed to achieve remission should be switched to another class of medicine.

The Panel considered that by not identifying which the 'current guidelines' were in the explanation itself readers might be misled. The claim could not stand alone without reference to the small print. A breach of the Code was ruled. The Panel further considered that the claim and its explanation gave a misleading impression of the Maudsley guidelines; these guidelines did not emphatically recommend that if a patient failed to achieve remission they should be switched to another class of medicine. Breaches of the Code were ruled.

Lundbeck referred to the claim 'Also for your depressed patients with General Aches & Pains (GAPs)' and noted that GAPs was not a medically defined condition within mood disorders. Clinicians might associate the company-generated acronym, in the context of depression, with GAD (generalised anxiety disorder) or SAD (social anxiety disorder) or wrongly conclude that Cymbalta could be used as an analgesic or to treat pain which in itself could lead to secondary depression. In addition, Lundbeck alleged that the claims and inferences that Cymbalta possessed some special property or merit compared with other antidepressants in the treatment of somatic symptoms of depression (including painful symptoms) was misleading. Any and all antidepressants would relieve the somatic symptoms by treating the underlying depression.

The Panel did not consider that GAP would be confused with GAD or SAD nor did it accept that the materials implied that Cymbalta could be used to treat painful conditions that might lead to depression. No breach of the Code was ruled. Although the Cymbalta summary of product characteristics (SPC) stated that the product was statistically more effective than placebo in bringing about an improvement in a depression rating scale (including both emotional and somatic symptoms) the Panel considered that the claim 'also for your depressed patients with General Aches and Pains (GAPs)' went beyond that and implied special merit, was inconsistent with the marketing authorization, misleading and incapable of substantiation. Breaches of the Code were ruled.

Lundbeck referred to a page in the detail aid in which the claim 'Cymbalta 60mg OD also treated the General Aches and Pains in depressed patients' was followed by a graph, adapted from Fava *et al* (2004), illustrating statistically significant improvements with Cymbalta compared with placebo in overall pain, back pain, shoulder pain, interference with daily activity and pain while awake. Lundbeck alleged that this page further reinforced the conclusion that Cymbalta treated general aches and pains by acting as an analgesic. Lundbeck noted that the design of Fava *et al* was such that a multitude of confounding factors could easily account for the effects seen. By taking inappropriate credit for the improvements in the secondary outcome measure, the properties of Cymbalta had been portrayed in a misleading and unsubstantiated manner.

The Panel did not consider that the page implied that Cymbalta acted as an analgesic as alleged. However, the limitations of Fava *et al* had not been given ie the exclusion of patients with combined medical and psychiatric conditions; the use of a visual analogue scale to assess pain severity was not as well established as standardized questionnaires; limited use of some hypnotics for insomnia was allowed as was episodic use of prescription analgesics. The Panel considered that the page was misleading in that the results were presented as being definitive. The data did not support the impression given which was not capable of substantiation. Breaches of the Code were ruled.

The claims 'Successful symptom resolution (remission) is an important goal of treatment in depression' and 'Treating a broader range of depressive symptoms may lead to more patients experiencing successful symptom resolution' appeared on page 2 of the detail aid. The claim 'Reduced levels and imbalance of Action Balance', a scale showing Cymbalta to have an almost balanced reuptake binding ratio and the claim 'In pre-clinical studies Cymbalta is relatively balanced in its binding to 5-HT and NA reuptake sites' appeared on page 5 of the detail aid. Lundbeck alleged that these claims would lead clinicians to conclude that successful symptom resolution ie remission was an important goal of treatment. This claim was further reinforced by the bold, inaccurate and untrue claim that 'Current guidelines for the treatment of depression state that if a patient fails to achieve remission on an antidepressant, they should be switched to another class of drug'. The claims in the detail aid inferred that the medicine with the best

chance of remission was one that addressed a broad range of symptoms. The medicine best placed to address this broad range of symptoms was one that redressed the reduced levels and an imbalance of serotonin (5-HT) and noradrenaline (NA) ie Cymbalta with its 'balanced' dual action. Lundbeck alleged that this emphasis on balance disparaged SSRIs. There was neither any clinical evidence to support the claim that SSRIs were less effective in treating patients with major depressive episodes than Cymbalta, nor that Cymbalta 60mg od had a genuine 'dual' action at 5-HT and NA reuptake sites in patients with a major depressive episode beyond what had been extrapolated from pre-clinical studies. Lundbeck considered that it should have been made clear that the claim that 'Reduced levels and imbalance of 5-HT and NA are thought to be responsible for the psychological and somatic symptoms experienced by many patients with depression' was derived from a theory and not from a clinical trial and as such could not be extrapolated into the clinical setting.

The Panel noted that pages 1-5 of the detail aid set out the arguments for treating depression and the role of 5-HT and NA. A hypothetical neurobehavioural model, based on mostly animal data, of symptoms mediated by 5-HT and NA was included on page 3. This was followed by the claim 'Reduced levels and imbalance of 5-HT and NA are thought to be responsible for the psychological and somatic symptoms experienced by many patients with depression.' Pages 4 and 5 referred to binding affinities and ratios of the newer antidepressants giving details for fluoxetine, venlafaxine, Cymbalta and reboxetine. The Panel considered that it was not necessarily unacceptable to provide information about the mechanism of action of Cymbalta including *in vitro* information. Although pages 3, 4 and 5 were labelled as being based on either animal or preclinical data this was misleading due to the reference to 'patients' on page 3. Further the relevance and significance to the clinical situation had not been established. Readers would interpret the data as applying to the clinical situation. Breaches of the Code were ruled.

The Panel did not consider that the detail aid disparaged SSRIs. There was no implication that SSRIs were inferior treatments for depression compared to a balanced medicine. Nor that SRRIs did not address a broad range of symptoms and hence lead to remission of symptoms. The Panel ruled no breach of Code.

Lundbeck alleged that the claim 'As early as week 1 Cymbalta provided significant relief ($P<0.05$) of depressed mood' was misleading; readers might assume that it related to the total depression score and not just a sub-item of it. In addition, there were other sub-items which were statistically significantly in favour of placebo at week one; to not mention these meant that the data had not been reflected in an accurate and balanced manner. Lundbeck further alleged that claims for somatic symptom relief were unsubstantiated.

The Panel considered that the claim at issue was clearly about one item of the total depression score. The Panel considered that the position was sufficiently clear. No breach of the Code was ruled. The Panel also did not consider it misleading to omit differences which were statistically significantly in favour of placebo at week 1. No breach of the Code was ruled. With regard to the claims about somatic symptom relief, the Panel noted that confusion had arisen due to a typing error on a poster. The claims, however, accurately reflected the data. No breach of the Code was ruled.

Lundbeck alleged that the claim 'No blood pressure monitoring is recommended in patients without pre-existing hypertension or cardiac disease' was misleading through the confusing use of a double negative. On balance the Panel agreed and also considered that the claim was not a fair reflection of the relevant statement in the SPC. A breach of the Code was ruled.

Lundbeck Ltd complained about the promotion of Cymbalta (duloxetine) by Eli Lilly and Company Limited and Boehringer Ingelheim Limited. The items at issue were a detail aid (DDP120/Dec 2004) and a dosing guide (DDP149/Dec 2004). Each was used with general practitioners and other health professionals in primary care. Cymbalta was a combined serotonin and noradrenaline reuptake inhibitor (SNRI) indicated for treatment of major depressive episodes.

Lundbeck supplied Cipramil and Cipralex, both were selective serotonin reuptake inhibitors (SSRIs) indicated, *inter alia*, for the treatment of depression.

1 Claim 'An option for depressed patients failing to respond to an SSRI' supported by the explanation 'Current guidelines for the treatment of depression state that if a patient fails to achieve remission on an antidepressant, they should be switched to another class of drug'

The claim and explanation each appeared on page 13 of the detail aid and page 1 of the dosing guide. The explanation was referenced to The Maudsley 2003 Prescribing Guidelines.

COMPLAINT

Lundbeck alleged that the phrase 'Current guidelines' misled by implication as clinicians might interpret it to mean the guidelines on the management of depression issued by the National Institute for Clinical Excellence (NICE) in December 2004. The cited reference, however, was The Maudsley 2003 Prescribing Guidelines, which only incorporated information up to April 2003. The Maudsley guidelines were thus almost two years old, and were neither the most current nor the most authoritative guidelines on the treatment of depression.

The NICE guidelines represented the most authoritative current source of recommendations on the appropriate treatment and care of patients with specific diseases and conditions within the NHS in England and Wales. Nationally, health professionals were expected to take it into account when exercising their clinical judgement. The NICE guidelines were

developed by groups of expert health professionals, lay representatives and those with technical expertise, in collaboration with a wide range of registered stakeholders and based on the best available evidence. They represented the gold standard and should be the first point of reference when quoting documented treatment advice.

Lundbeck noted that when clinicians considered a limited response to pharmacological treatment, the NICE guideline recommended:

- 'Consider switching to another antidepressant if there has been no response after a month. If there has been a partial response, a decision to switch can be postponed until 6 weeks.
- If an antidepressant has not been effective or is poorly tolerated and, after considering a range of other treatment options, the decision is made to offer a further course of antidepressants, then switch to another single antidepressant.
- Choices for a second antidepressant include a different SSRI or mirtazapine; alternatives include moclobemide, reboxetine and tricyclic antidepressants (except dosulepin)…'.

Lundbeck stated that the NICE guideline emphatically did not recommend clinicians change class if a patient on an SSRI did not achieve remission.

Lundbeck alleged that in addition to the misleading nature as to the source of the current guidelines, the promotional claims were an unfaithful representation of what the Maudsley guidelines actually recommended. Lundbeck noted that the Maudsley guidelines stated that an antidepressant from a different class should only be given if either there was no effect, or the current medicine was poorly tolerated. This advice was further qualified by the sentence 'there is some evidence that switching within a drug class can be effective' and from page 143 onwards the subsequent pages illustrated how to swap different medicines within the same class of SSRIs. This advice was inconsistent with the material at issue which stated that unless a patient achieved remission, they should be switched to another class of medicine. There was a significant clinical magnitude of difference between no effect (=no response) and remission, and paradoxically this was amply illustrated on page 2 of the detail aid.

Lundbeck alleged that the claims at issue were not a fair reflection of the Maudsley guidelines, and were an inaccurate and unsubstantiated representation of the facts. The claims were also inconsistent with the current most up-to-date evaluation of all the evidence ie the NICE Guideline. High ethical standards had not been upheld.

Breaches of Clauses 7.2, 7.4 and 9.1 of the Code were alleged.

RESPONSE

Lilly and Boehringer Ingelheim submitted that it was appropriate to cite the Maudsley guidelines which were long established guidelines, now in their seventh edition. The material referred to the current edition of the Maudsley guidelines and it was in that context that the word 'current' was used, and whilst the companies recognised that the NICE guideline was important, they disagreed with Lundbeck that the term 'current guidelines' either implied or necessitated reference to the NICE guideline. Lundbeck ignored the fact that the scope for the NICE Guideline was issued in 2001, and the cut-off date for literature searches for systematic review was April 2003 or earlier.

The companies noted that the NICE Guideline was restricted to England and Wales, whereas the marketing authorization for Cymbalta extended throughout the UK. The Maudsley guidelines were also free of geographic limitation. Consistent with these timings, there was no recommendation in respect of Cymbalta in the NICE guideline for the sole reason that it did not possess a marketing authorization at the time of review and was therefore not included.

The companies submitted that they had not directly quoted the Maudsley guidelines but paraphrased them. No quotation marks were used. Page 119 of The Maudsley guidelines indicated that if patients had shown no effect then they should be switched to a different class of treatment. The evidence and context for this recommendation was given in the footnote on page 119 of the Maudsley guidelines, which was only partially quoted in the Lundbeck complaint.

> 'Switching between drug classes in cases of poor tolerability is not well supported by published studies but has a strong theoretical basis. In cases of no response, there is some evidence that switching within a drug class can be effective, but switching between classes is, in practice, the most common option.'

The companies submitted that the question was therefore the interpretation of the term 'no effect'. The evaluation of 'effect' or 'no effect' in routine clinical practice would, at least in part, be subjective. Most clinicians considered that returning patients to a symptom free state (ie remission) was the required level of effect. Most courses of antidepressants would cause some alleviation of patients' symptoms; however, this might not be clinically acknowledged as adequate 'effect'. The companies submitted that, therefore, achieving remission, and achieving a clinical effect were one and the same, and as such they had represented the Maudsley guidelines accurately. It appeared that the NICE guideline shared similar views to Lilly and Boehringer Ingelheim with regard to 'no effect' and 'no remission' being interchangeable. The NICE guideline stated:

- 'If an antidepressant has not been effective or is poorly tolerated and, after considering a range of treatment options, the decision is made to offer a further course of antidepressants, then switch to another single antidepressant.
- Choices for second antidepressants include a different SSRI or mirtazepine, alternatives include moclobemide, reboxetine and tricyclic antidepressants (except dosulepin) …'.

The NICE guideline was consistent with the claim that Cymbalta 60mg od was 'An option for your

patients failing to respond to an SSRI'. Furthermore, the change to another medicine referred to in bullet point one above and the choices recommended in bullet three were also consistent with the promotion of Cymbalta.

In summary the companies submitted that the reference to the Maudsley guidelines as 'current guidelines' was appropriate and the materials were an accurate reflection of the guidelines. Furthermore, this representation was consistent with other guidelines such as NICE. The companies did not accept that they had breached Clauses 7.2, 7.4 or 9.1 of the Code.

PANEL RULING

The Panel noted that the NICE guideline applied in England and Wales. The Maudsley guidelines were well established and applicable to the whole of the UK.

The Panel considered that by not identifying what was meant by the phrase 'current guidelines' in the explanation itself readers might be misled. Although the information was given in the references to the explanation, this was not sufficient. The claim could not stand alone without reference to the small print. A breach of Clause 7.2 of the Code was ruled.

With regard to the Maudsley guidelines, the Panel noted that the schematic representation (page 119) recommended that when starting with an antidepressant, efficacy should be assessed over 4-6 weeks, then if there was no effect the dose should be increased followed by assessment over a further two weeks. If there was still no effect then an antidepressant from a different class should be given. A footnote stated that in the case of non-response there was some evidence that switching within a medicine class could be effective but switching between classes was in practice the most common option. The Maudsley guidelines did not use the term remission.

The Panel considered that it was not unreasonable to claim that Cymbalta was an option for patients failing to respond to an SSRI. It was however misleading to state that the Maudsley guidelines emphatically recommended that if a patient failed to achieve remission they should be switched to another class of medicine. The guidelines also recommended increasing the dose and raised the possibility of switching within a class. The Panel considered that the detail aid and the dosing card gave a misleading impression of the Maudsley guidelines. Breaches of Clauses 7.2 and 7.4 of the Code were ruled.

The Panel considered this ruling of breaches of Clauses 7.2 and 7.4 encompassed consideration of the requirements of Clause 9.1. Nonetheless given that an allegation of a breach of this clause had been made it was obliged to rule upon it and a breach of Clause 9.1 was thus ruled.

2 Claim 'Also for your depressed patients with General Aches & Pains (GAPs)'

The claim appeared on page 13 of the detail aid and page 1 of the dosing guide. The claim in the detail aid was referenced to the summary of product characteristics (SPC).

COMPLAINT

Lundbeck noted that GAPs was not a medically defined condition within mood disorders as part of either the ICD-10 or the DSM-IV classification of mental disorders. A clinician, especially in light of the reference to the SPC, might mistake GAPs to imply that Cymbalta was additionally licensed to treat depression with general aches and pains. In addition the clinician might also erroneously associate the company-generated acronym 'GAP', in the context of depression, with the similar sounding but authentic conditions such as GAD (generalised anxiety disorder) or SAD (social anxiety disorder), for which other antidepressants had additional marketing authorizations. The particulars listed in the Cymbalta SPC neither stated that it was licensed as an analgesic nor that Cymbalta possessed any special analgesic properties.

Lundbeck noted that Cymbalta's only licensed indication was for the treatment of major depressive episodes. A clinician might wrongly conclude that Cymbalta could be used to treat either patients with acute or chronic pain conditions without any depression (ie as an analgesic), or for the purpose of treating the underlying somatic pain eg chronic arthritic conditions that could lead to a secondary depressive episode.

Lunbeck had been unable to find the specific condition of the 'general aches and pains' or the acronym 'GAP' in any of the materials referenced to mention of 'GAPs' in the detail aid (Jones 1991; Stahl 2002; Ohayon *et al* 2003; Bair *et al* 2004; Fava *et al* 2004; Brannan *et al* 2005 and Hirschfeld *et al* 2004) or in the dosing card.

Lundbeck alleged that in addition the direct claims and indirect inferences that Cymbalta possessed some special property or merit compared with other antidepressants in the treatment of the somatic symptoms associated with depression (including painful symptoms) was in itself misleading. Many patients with major depressive disorder presented with somatic symptoms eg backache or muscle ache. Indeed clinicians, through the use of the HAMD-17 item depression rating scale, recorded these somatic symptoms and any subsequent improvement in somatic symptoms. The existence of somatic symptoms in depression was not new and there was extensive literature on the subject of pain and anxiety associated with depression. In relation to the somatic symptoms of depression, any and all antidepressants would relieve the somatic symptoms including pains associated with depression, by treating the underlying major depressive episode.

Lundbeck alleged that the term 'GAPs' was misleading and incapable of substantiation, and did not consider that Cymbalta had either a licence to be used as an analgesic to treat general aches and pains or a specific licence to support the claim 'also for depressed patients with General Aches & Pains (GAPs)'.

Lundbeck alleged breaches of Clauses 7.2, 7.4, and 3.2 of the Code.

RESPONSE

Lilly and Boehringer Ingelheim stated that nothing in the detail aid or the dosing card suggested that Cymbalta was indicated for any condition outside of depression. It was quite clear on all pages where claims related to effects on general aches and pains that this was in the context of patients with depression. For example, '…increase a depressed patient's sensitivity to general aches and pains' in the heading on page 8, or '… also treated the General Aches & Pains in depressed patients' on page 9 of the detail aid. The companies refuted the suggestion that Cymbalta was being promoted as an analgesic to treat general aches and pains outside the context of depression.

Whilst the companies accepted that general aches and pains was not an independent and defined condition such as generalised anxiety disorder, they noted that aches and pains were considered symptoms of major depression and the actual words aches and pains could be found in the context of major depression within the DSM-IV-TR, 'some individuals (with depression) emphasize somatic complaints eg bodily rather than reporting feelings of sadness'.

The companies submitted that whilst the published literature might not cite the term general aches and pains, there was clear recognition of a range of such symptoms in the context of depression. Ohayon *et al* examined chronic painful physical conditions in relation to major depression and specifically cited joint/articular, limb, or back pain, headaches or gastrointestinal diseases. Stahl referred to painful physical symptoms in depressed patients such as headache, abdominal pain, or musculoskeletal pain in the lower back, joints, and neck. Fava *et al* (2004) referred to painful physical symptoms and depressed patients with overall pain, headaches, back pain, shoulder pain, interference with daily activity, and time in pain while awake. In a separate publication Fava *et al* (2003) referred to depressed patients experiencing the general symptoms of pain and the vague physical complaints such as headache, backache, stomach ache, joint and muscle aches and chronic fatigue.

The use of the term general aches and pains to describe this particular set of somatic symptoms experienced by depressed patients was legitimate and could be substantiated. This also seemed to be recognised by Lundbeck as it stated that many patients with major depressive disorder presented with somatic symptoms eg backache or muscle ache.

The companies submitted that there was thus clear recognition that many depressed patients experienced aches and pains. The licensed indication for Cymbalta was 'major depressive episodes', and this included the broad range of symptoms found in depressed patients including, for example, anxiety symptoms of depression (though not generalised anxiety disorder which was a distinct condition), as well as the somatic symptoms of depression, which clearly included general aches and pains.

The companies submitted that, therefore, its discussion of general aches and pains, which was always contextualised as being part of the range of symptoms of depression, fell within the terms of their marketing authorization for major depression. Section 5.1 of the Cymbalta SPC, included the statement that the product demonstrated statistical superiority over placebo as measured by improvement in the 17-item HAMD total score (including both the emotional and somatic symptoms of depression).

The companies noted that in the context of the symptoms of depression in which general aches and pains were clearly presented in its promotional materials, clinicians would not be led to believe that general aches and pains was a condition separate and distinct from depression.

The companies submitted that in the materials did not imply that Cymbalta might have analgesic properties for patients with acute or chronic pain. Neither was there any mention or implication that Cymbalta would be beneficial in pain conditions that might lead to a secondary depressive episode.

There was no claim that Cymbalta possessed unique properties in the treatment of general aches and pains in depression.

In summary, where the effects of Cymbalta on general aches and pains were referred to it was always clearly stated that this was in patients with depression. No statements implying or inferring general analgesic properties were made. There was wide recognition that aches and pains were somatic symptoms of depression and this was further reflected in the inclusion of a specific question to this effect in the HAMD-17. The companies denied breaches of Clauses 7.2, 7.4 and 3.2.

PANEL RULING

The Panel noted Lilly and Boehringer Ingelheim's submission that although general aches and pains was not an independent and defined condition, they were considered symptoms of major depression and that some patients with depression emphasized somatic complaints eg aches and pains rather than reporting feelings of sadness.

The Panel noted that Section 5.1 of the Cymbalta SPC stated that 'Cymbalta demonstrated statistical superiority over placebo as measured by improvement in the 17-item Hamilton Depression Rating Scale (HAM-D) total score (including both the emotional and somatic symptoms of depression)'.

The Panel noted that both the detail aid and the dosing card clearly stated that Cymbalta was for the treatment of depression. The first mention of general aches and pains in the detail aid was in a proposed model of symptoms mediated by 5HT (serotonin) and NA (noradrenaline) (page 3). In addition, general aches and pains were mentioned on pages 8, 9, 12 and 13 (point 3 below related to page 9 of the detail aid). The dosing card included the claim 'Also for depressed patients with General Aches & Pains (GAPs)' as a final bullet point beneath the heading 'For the treatment of depression'.

The Panel did not consider that the term general aches and pains (GAP) would be confused with GAD (generalized anxiety disorder) or SAD (social anxiety disorder) for which other antidepressants were licensed. The Panel did not accept that the impression was given that Cymbalta could be used to treat pain conditions that might lead to depression. No breach of Clauses 3.2, 7.2 and 7.4 was ruled with regard to the detail aid and the dosing card.

The Panel considered that neither the detail aid nor the dosing card gave the impression that general aches and pains were not associated with depression. However, it considered that the claim went beyond the information given in the SPC about Cymbalta's effect on the somatic symptoms of depression and implied special merit in that regard. The Panel considered that the claim was inconsistent with the marketing authorization, misleading and incapable of substantiation and ruled breaches of Clauses 3.2, 7.2 and 7.4 of the Code.

3 Claim 'Cymbalta 60mg OD also treated the General Aches & Pains in depressed patients'

The claim appeared on page 9 of the detail aid and was followed by a graph illustrating statistically significant improvements with Cymbalta compared with placebo in overall pain, back pain, shoulder pain, interference with daily activity and pain while awake. The graph was adapted from Fava *et al* (2004).

COMPLAINT

Lundbeck alleged that this page further reinforced the conclusion that Cymbalta treated general aches and pains by acting as an analgesic. A clinician looking at the graph would conclude that Cymbalta could singularly take responsibility for the improvements observed. Lundbeck stated that flawed logic was used in the detail aid as follows:

Premises:

- Patients with major depressive episodes had psychological, biological and somatic symptoms
- Baseline pain in 6 categories (the category of headache had not been illustrated) was measured
- Patients treated with Cymbalta showed a statistically significant improvement in the primary outcome measure of the overall HAM-D score compared to placebo
- Improvements that were statistically significantly better than placebo (as measured by the visual analogue scale (VAS) score) are also presented under the heading 'Cymbalta 60mg OD also treated the General Aches and Pains in depressed patients'

Conclusion:

The improvements seen were due to Cymbalta.

However, Lundbeck noted that none of the patients measured by the VAS score were selected or even randomized according to the type, severity, chronicity or even the presence of pain. As such there was a multitude of confounding factors that could easily account for the effects seen.

Lundbeck noted that the trials did not record what had caused the pain eg acute or chronic pain unrelated to depression, and the alleviation in pain seen could easily be accounted for by the episodic use of prescription-only analgesic agents as specified in the study design methodology particularly with the baseline levels of pain being relatively low (<28 out of a 100 on the VAS score). Lundbeck inferred that the continuous or episodic use of over-the-counter medicines, eg ibuprofen or paracetamol was also permissible.

Lundbeck alleged that by taking inappropriate credit for the improvements seen in the secondary outcome measure of the VAS score, the properties of Cymbalta had been portrayed in a misleading and unsubstantiated manner. High standards had not been maintained, by portraying Cymbalta to clinicians as having analgesic properties and/or a special merit that it did not possess.

Breaches of Clauses 7.2, 7.4 and 9.1 of the Code were alleged.

RESPONSE

Lilly and Boehringer Ingelheim refuted the suggestion that the graph implied that Cymbalta acted as a typical analgesic. It was clearly stated in the heading that the graph showed data for depressed patients who had aches and pains. The data presented was substantiated by peer reviewed publications of randomized, controlled, double-blind studies. Both groups (placebo and duloxetine) were similar at baseline with respect to demographics and psychiatric history, which included an assessment of HAMD 17 and pain associated with depression (as measured by VASs).

Patients in the studies were not selected on the basis of pain but on the basis of the presence and severity of depression based on the strict Mini-International Psychiatric Interview (MINI). It was important to note that patients with medical conditions were excluded from this study in order to make the sample as pure for depression as possible and reduce confounding factors.

The companies submitted that given that randomization therefore was successful, and that the blind was maintained through these regulatory grade studies, it was reasonable to assume that differences between the groups on the VAS were due to the active treatment. This was entirely consistent with any claim made on the basis of any well conducted randomized double-blind methodology for any active treatment.

In summary, the claim that 'Cymbalta 60mg OD also treated the General Aches & Pains in depressed patients' accurately reflected the clinical trial data. Improvement in pain was reflected in the HAMD 17 (item 13) and was further explored and confirmed by VAS pain assessments. Section 5.1 of the Cymbalta SPC included the statement that Cymbalta demonstrated statistical superiority over placebo as measured by improvement in the 17-item HAMD total score (including both emotional and somatic symptoms of depression). The data were derived

from well conducted randomized controlled studies in patients in whom other medical conditions which could cause pain among other things, were excluded. The companies denied breaches of Clauses 7.2, 7.4 and 9.1.

PANEL RULING

The Panel noted that Fava *et al* (2004) pooled efficacy data from two, 9 week randomized, double-blind clinical trials of duloxetine and placebo. All patients met diagnostic criteria for major depressive disorder. The primary efficacy measure was the Hamilton Rating Scale for Depression (HAMD-17) total score. Secondary outcome measures included the Clinical Global Impressions – Severity of Illness (GGI-S), the Patient Global Impression of Improvement (PGI-I), the Somatic Symptom Inventory (SSI), the Quality of Life in Depression Scale (QLDS) and Visual Analogue Scales (VAS) for pain (overall pain, headaches, back pain, shoulder pain, interference with daily activities and time in pain while awake). The study examined the hypothesis that the resolution of both psychological and physical symptoms of depression would predict a higher percentage of patients achieving remission. Fava *et al* (2004) concluded that the results established the efficacy of duloxetine as a treatment for both the psychological/emotional symptoms of depression and the painful physical symptoms associated with major depressive disorder. The analysis demonstrated that 50% of the improvement in pain was independent of improvements in depression and that the improvements in pain severity were associated with more favourable depression treatment outcomes including higher rates of remission, improved quality of life and improved clinical and patient related global outcomes. Further investigations were needed to confirm the findings. The results emphasized the importance of adequately treating painful physical symptoms and the potential role such treatment might play in achieving higher overall rates of remission.

Patients in the study were not required to meet a minimum threshold at baseline for pain and the studies were not powered for pain outcomes.

Fava *et al* stated that it was difficult to address the question of whether the alleviation of painful physical symptoms was associated with higher remission rates in a prospectively defined study. These post hoc analyses provided compelling evidence that, independent of changes in the core emotional symptoms of depression, alleviation of painful symptoms was associated with greater probabilities of remission. One of the study's strengths was that patients displayed a spectrum of pain severity (mean baseline score 27/100, individual base line score ranged from 0-97). The fact that widespread associations between pain severity improvement and depressive symptom improvement using a variety of techniques in a population of relatively low baseline pain severity was noteworthy. The limitations of the study included uncertainty with regard to the generalisation of the results in that patients with many comorbid medical and psychiatric conditions were excluded. The use of VAS to assess pain severity was not as well established as standardized questionnaires. Concomitant medication with primarily central nervous system activity was not allowed with the exception of limited use of chloral hydrate or zolpidem for insomnia. Chronic use of prescription pain medication was not allowed. Episodic use was permitted. There was no mention about use of over-the-counter medicines for pain.

The Panel did not consider that the page implied that Cymbalta acted as an analgesic. The heading referred to depressed patients as did the claim beneath the graph. The patients in the study all had major depressive disorder.

The Panel considered that the data would be of interest to clinicians. It noted its rulings in point 2 above. The page now at issue went beyond the statement in the SPC. The limitations of the study had not been given and thus the results could not be properly assessed. The Panel considered that the page was misleading in that the results were presented as being definitive. The data did not support the impression given which was not capable of substantiation. The Panel ruled breaches of Clauses 7.2 and 7.4.

The Panel considered that this ruling of a breaches of Clauses 7.2 and 7.4 encompassed consideration of the requirements of Clause 9.1. Nonetheless given that an allegation of a breach of this clause had been made it was obliged to rule upon it and a breach of Clause 9.1 was thus ruled.

4 Claims for dual action based on *in vitro* data extrapolated to the clinical situation. Claims that Cymbalta is a balanced medicine

The claims 'Successful symptom resolution (remission) is an important goal of treatment in depression' and 'Treating a broader range of depressive symptoms may lead to more patients experiencing successful symptom resolution' appeared on page 2 of the detail aid.

The claim 'Reduced levels and imbalance of 5-HT and NA are thought to be responsible for the psychological and somatic symptoms experienced by many patients with depression' and the heading '5-HT and NA are thought to mediate a broad range of depressive symptoms' appeared on page 3 of the detail aid.

The heading 'Cymbalta Mechanism of Action Balance', a scale showing Cymbalta to have an almost balanced reuptake binding ratio and the claim 'In pre-clinical studies Cymbalta is relatively balanced in its binding to 5-HT and NA reuptake sites' appeared on page 5 of the detail aid.

COMPLAINT

Lundbeck alleged that the above claims would lead clinicians to conclude that successful symptom resolution ie remission was an important goal of treatment. This claim was further reinforced by the bold, inaccurate and untrue claim that 'Current guidelines for the treatment of depression state that if a patient fails to achieve remission on an antidepressant, they should be switched to another class of drug'. The claims in the detail aid inferred

that the medicine with the best chance of remission was one that addressed a broad range of symptoms. The medicine best placed to address this broad range of symptoms was one that redressed the root cause of these symptoms, ie reduced levels and an imbalance of serotonin (5-HT) and noradrenaline (NA). The best way of treating the imbalanced and reduced levels of 5-HT and NA was with Cymbalta and its 'balanced' dual action.

Lundbeck alleged that the emphasis on balance disparaged SSRIs (eg escitalopram with a NA/5-HT Ki ratio of more than 7000 (Owens *et al* 2001) and thus could be considered extremely imbalanced), as by implication a medicine that was imbalanced (by not preventing the NA re-uptake) was not as effective in redressing the imbalance and the reduction in 5-HT and NA. Following the claims made in the detail aid, one concluded that the prescription of an imbalanced medicine was less likely to lead to remission in patients with a major depressive episode. In effect, the claims stated that selective unbalanced SSRIs were not as good in treating patients with depression as balanced medicines. There was also the inference through the diagram on page 3 that SSRIs could not address the symptoms of concentration, energy, motivation and vigilance caused by a reduction/ imbalance in NA. Lundbeck noted from Reines *et al* (2002) that escitalopram was effective in relieving the symptoms of concentration difficulties and lassitude (lack of energy) as measured by the sub-items on the Montgomery Asberg depression rating scale. There was neither any clinical evidence to support the claim that SSRIs were less effective in treating patients with major depressive episodes than Cymbalta, nor that Cymbalta 60mg od had a genuine 'dual' action at 5-HT and NA reuptake sites in patients with a major depressive episode beyond what had been extrapolated from pre-clinical studies.

Lundbeck alleged that the claims listed could not be extrapolated to the clinical setting, and that the emphasis on balanced action as portrayed in the detail aid with the supporting claims disparaged 'imbalanced' medicines ie SSRIs.

The claim that Cymbalta had a true dual action in patients with major depressive episodes at 60mg od was exaggerated and incapable of substantiation. The NICE Guideline stated that the dual action of venlafaxine, another SNRI, only occurred at doses of 150mg or higher per day, and there was no clinical evidence to suggest that Cymbalta had a dual action at 60mg per day.

Lundbeck considered that it should have been made clear that the misleading claim on page 3 that 'Reduced levels and imbalance of 5-HT and NA are thought to be responsible for the psychological and somatic symptoms experienced by many patients with depression' was derived from a theory and not from a clinical trial setting, and as such could not be extrapolated readily into the clinical setting. Ressler *et al* (2003), referenced on page 3, stated that the evidence currently seemed more in support of overall increased NA activity in depression and anxiety. This clearly implied an increased level of NA leading to symptoms of depression and not (as claimed) a decreased level of NA.

Lundbeck alleged that the claim that Cymbalta 60mg od acted as a true dual inhibitor in patients with major depressive episodes was misleading and could not be substantiated. Claims that a balanced action was somehow more desirable than an imbalanced medicine disparaged SSRIs (eg escitalopram) and could not be substantiated in the clinical setting.

Lundbeck alleged breaches of Clauses 7.2, 7.4 and 8.1 of the Code.

RESPONSE

Lilly and Boehringer Ingelheim stated that the pre-clinical data referred to was presented on pages 3, 4 and 5 of the detail aid. Great care had been taken not to extrapolate pre-clinical data to any potential clinical benefit. In the detail aid, the pre-clinical pages describing the mode of action of Cymbalta were placed in a double page spread and clinical data was placed separately, later in the detail aid.

In addition, where pre-clinical or animal data had been used this had been clearly and unambiguously stated. The companies therefore rejected Lundbeck's contention that they had extrapolated non-human data into benefits for patients. They were obliged to tell health professionals about the mode of action of this new antidepressant. The companies' view was that the structure and content of the materials at issue had clearly delineated pre-clinical from clinical data.

There was no claim or statement suggesting that SSRIs were any less effective in treating depression. The balance chart (page 5) depicted the pre-clinical pharmacology of different antidepressants. The activities at each end of the balance represented pharmacological activity proven to be effective in the management of depression. The diagram showed that Cymbalta was more balanced in its effects on these two well accepted mechanisms of antidepressant activity and showed the relative balance compared with venlafaxine, the only other approved member of this pharmacological class of antidepressant agents.

Nowhere in the detail aid had 'balanced' been applied to Cymbalta clinical data and nor was it implied that Cymbalta had been clinically demonstrated to act in a balanced way. It was not suggested that SSRIs were not clinically beneficial across the range of symptoms of depression or that they were not effective treatments for depression. It was not suggested that Cymbalta was superior to SSRIs. Indeed, page 13 of the detail aid stated that Cymbalta was 'An option for your patients failing to respond to an SSRI'. In other words the companies accepted that SSRIs were first line treatment in moderate/severe depression and, hence, must have clinical benefit.

The companies rejected Lundbeck's allegation that describing Cymbalta's mode of action as balanced disparaged SSRIs.

The words 'true' and 'dual' were not in the detail aid. None of the pages of the materials that examined Cymbalta clinical data mentioned mode of action, serotonin or noradrenaline. The only reference to the mode of action was made on the pages which legitimately described the pharmacodynamic properties of Cymbalta. This was consistent with the

SPC, which confirmed that duloxetine was a combined 5-HT and NA reuptake inhibitor (section 5.1).

In summary the presentation of information relating to the effect of Cymbalta on serotonin and noradrenaline was accurate and consistent with the SPC. Pharmacological data of this type was based, necessarily, on pre-clinical studies and it was clearly shown in the detail aid that these were pre-clinical data. This information had been separated from the clinical information. The use of the word balance in respect of Cymbalta was only used in the context of pre-clinical studies and in terms of the ratio of binding to 5-HT and NA receptors. There was no extrapolation to the clinical setting. No clinical claims were made based upon pre-clinical data, no claims inferring special merit for a balanced medicine and no statements disparaging SSRIs were made. The companies denied breaches of Clauses 7.2, 7.4 or 8.1.

PANEL RULING

The Panel noted that pages 1-5 of the detail aid set out the arguments for treating depression and the role of 5-HT and NA. A hypothetical neurobehavioural model of symptoms mediated by 5-HT and NA was included on page 3. The model was based on mostly animal data. This was followed by the claim 'Reduced levels and imbalance of 5-HT and NA are thought to be responsible for the psychological and somatic symptoms experienced by many patients with depression'. Thus the Panel did not accept the submission that the pre-clinical data had not been extrapolated to any potential clinical benefit. The Panel was also unsure as to the relevance of the description of the dual action of Cymbalta as 'balanced'. Pages 4 and 5 referred to binding affinities and ratios of the newer antidepressants giving details for fluoxetine, venlafaxine, Cymbalta and reboxetine. The Panel considered that it was not necessarily unacceptable to provide information about the mechanism of action of Cymbalta including *in vitro* information. Although pages 3, 4 and 5 were labelled as being based on either animal or preclinical data this was misleading due to the reference to 'patients' on page 3. Further the relevance and significance to the clinical situation had not been established. Readers would interpret the data as applying to the clinical situation. Breaches of Clauses 7.2 and 7.4 of the Code were ruled.

There was no actual claim that Cymbalta had a true dual action in major depressive episodes as implied by Lundbeck. Nor did the Panel accept that readers would be left with the impression that Cymbalta had a true dual action. Thus the Panel ruled no breach of Clauses 7.2 and 7.4.

The Panel did not consider that the detail aid disparaged SSRIs. There was no implication that SSRIs were inferior treatments for depression compared to a balanced medicine. Nor that SSRIs did not address a broad range of symptoms and hence lead to remission of symptoms. With regard to the Venn diagram on page 3 of the detail aid, there was no implication that SSRIs could not address the symptoms of concentration, energy, motivation or vigilance ie those hypothetically attributed to NA. It was clear that the model was a proposed model and that the reduced levels and imbalance of 5-HT and NA were thought to be responsible for psychological and somatic symptoms. The Panel ruled no breach of Clauses 7.2, 7.4 and 8.1.

5 Claim 'As early as week 1 Cymbalta provided significant relief ($p<0.05$) of depressed mood'

The claim appeared on page 7 of the detail aid and was referenced to Hirschfeld *et al*.

COMPLAINT

Lundbeck alleged that claim was misleading as a clinician might assume it meant the actual total depression score measured by the HAMD-17 item depression rating scale, ie the primary outcome measure of the study, being statistically significant from week one onwards, whereas it was only in an individual sub-item called 'depressed mood' that this was so. The placebo-treated group actually had a statistically significant improvement compared to Cymbalta in the sub-items 'somatic symptoms' and 'weight loss' (ie less weight loss due to improvements in the patient's medical condition) at week one and as such this claim did not reflect the available evidence in an accurate, fair and balanced manner.

Lundbeck could not verify the unsubstantiated claims made in the subsequent table labelled 'somatic symptom relief' as these were neither referenced by Hirschfeld *et al* nor by any of the other references on the page.

Lundbeck alleged that the claim that Cymbalta provided significant relief of depressed mood as early as week 1 was misleading and the somatic symptom relief claims were incapable of substantiation in breach of Clauses 7.2 and 7.4 of the Code.

RESPONSE

Lilly and Boehringer Ingelheim rejected Lundbeck's assertion that the data presented on depressed mood, which was item 1 of the HAM-D could be confused by clinicians to mean the Total Score HAM-D_{17}. On the opposing page (page 6) there was a graph clearly labelled HAM-D_{17} Total Score, and showed that for the Total Score, statistical separation occurred at week 2. Given the prominence of the graph, it was unlikely that clinicians would be confused. On page 7 the table in question was clearly labelled 'Depressive Symptom (HAM-D_{17} Item)'. Again this should leave no clinician under any ambiguity that the table and the claim at issue which appeared between the tables referred to key individual items of the HAM-D scale.

The companies submitted that Lundbeck had wrongly suggested that they were making week 1 claims across all the items represented in the tables on page 7. There was no potential for confusion as the heading of the second column of each of the tables clearly stated that significance at endpoint (week 9) was being presented.

The companies strongly rejected Lundbeck's claim that they had not reflected efficacy in somatic

symptoms in a fair and balanced manner. As could be clearly seen in the referenced material (Hirschfeld *et al* (early, middle and late)) Cymbalta statistically separated at endpoint over the following items in the HAM-D: insomnia early; insomnia middle; insomnia late; retardation; somatic symptoms/gastrointestinal; somatic symptoms/general and genital symptoms.

The companies submitted that given the results illustrated, the selection of items clearly reflected the benefits demonstrated in the data across the wider range of somatic symptoms and that the claims in the detail aid were fully substantiated by the data. A degree of confusion might have been caused by a typing error on the Hirschfeld poster. In the tables in the poster, the label 'weeks' should have read 'visits'. There were 6 visits in this 9 week study. The final column represented the endpoint of the study, week 9, which was the claim made in the detail aid.

This typing error notwithstanding, all the claims made on the second table were entirely substantiated.

In summary, the claim that 'As early as week 1 Cymbalta provided significant relief ($p<0.05$) of depressed mood' was accurate and was substantiated by the clinical data. The companies disagreed with the complainant that this might be interpreted as total depression score as the tabular presentation was clearly labelled and the total depression score was graphically displayed on the facing page. The companies denied breaches of Clauses 7.2 and 7.4.

PANEL RULING

The Panel noted that depressed mood was one of the 17 items used to make up the HAM-D total score. Page 6 set out the data for HAM-D total score. Page 7 showed data from various items including depressed mood. The Panel decided the position was sufficiently clear. Hirschfeld *et al* supported the data. No breach of Clauses 7.2 and 7.4 of the Code was ruled.

The Panel considered that it was not misleading to omit the differences that were statistically significantly in favour of placebo at week 1. These being somatic symptoms/gastrointestinal and loss of weight. At visit 6 (week 9) somatic symptoms/gastrointestinal was statistically significantly in favour of Cymbalta. From visit 6 until visit 9 there was no statistically significant difference between placebo and Cymbalta with regard to loss of weight. No breach of Clauses 7.2 and 7.4 of the Code was ruled.

With regard to the table headed 'Somatic symptom relief' the Panel noted Lilly and Boehringer Ingelheim's submission that there was a typing error on the Hirschfeld poster whereby the column headed 'week' should have been headed 'visit'. The corresponding data in the detail aid was labelled 'Cymbalta vs placebo at endpoint (week 9)'. The detail aid accurately reflected the statistically significant data for insomnia (early and late), retardation and general somatic in the Hirschfeld poster. In the circumstances the Panel did not consider that the somatic symptom claims were misleading or incapable of substantiation as alleged. No breach of Clauses 7.2 and 7.4 of the Code was ruled.

6 Claim 'No blood pressure monitoring is recommended in patients without pre-existing hypertension or cardiac disease'

The claim appeared on page 11 of the detail aid.

COMPLAINT

Lundbeck alleged that the use of the double negative was misleading; the claim might lull a clinician into falsely believing that no blood pressure monitoring was required at all.

Section 4.4 Special warnings and special precautions for use of the Cymbalta SPC, stated 'In patients with known hypertension and/or other cardiac disease, blood pressure monitoring is recommended as appropriate', ie it should be done in patients with these conditions. Venlafaxine, the other SNRI, had an even more restrictive marketing authorization, in that it was contraindicated in patients with hypertension and/or heart disease, and that in normotensive patient's blood pressure monitoring on a regular basis was mandatory.

Lundbeck considered that the warning as stated in Section 4.4 of the Cymbalta SPC should be clearly and unambiguously stated. The claim made was an inaccurate representation of what the warning was meant to convey to clinicians. The Cymbalta European Public Assessment Report (EPAR) (page 31) stated that the marketing authorization holder had undertaken to provide the Committee for Medicinal Products for Human Use (CHMP) with further data on the effect of Cymbalta in a sub-group of patients with a pre-treatment diastolic BP ≥ 90mmHg, and that patients treated with Cymbalta had a statistically significantly higher pulse rate and systolic blood pressure compared to those treated with placebo. A future class effect warning to monitor the BP in all patients similar to that which was stated in the SPC of venlafaxine could not be excluded.

Cymbalta was not the same as the SSRIs where no blood pressure monitoring was necessary. Lundbeck did not consider that the warning in section 4.4 of the Cymbalta SPC had been conveyed to clinicians in an unambiguous manner. The lack of a clearly stated warning might endanger the safety of patients and high standards had not been upheld. Lundbeck alleged breaches of Clauses 7.2 and 9.1 of the Code.

Lundbeck stated that taking these points as a whole, it was concerned over the way in which the Lilly and Boehringer Ingelheim representatives might have been briefed to use these promotional materials. If the promotion Cymbalta to clinicians was based upon and utilised the materials and claims contained within the detail aid and dose card, then the logical conclusion would be that the associated briefing documents might also be in breach of the Code.

RESPONSE

Lilly and Boehringer Ingelheim refuted these allegations. Cymbalta was a new antidepressant. The existing dual acting antidepressant, venlafaxine, had a stringent requirement for blood pressure monitoring in all patients, which was widely recognised by

prescribers (Efexor SPC). Cymbalta had a recommendation for blood pressure monitoring only in patients with pre-existing hypertension or cardiac disease (Cymbalta SPC). It was therefore important to clarify for prescribers the difference in requirement for blood pressure monitoring between venlafaxine and Cymbalta and in the companies' view this was most clearly done by the wording in the detail aid. That SSRIs had no requirement for blood pressure monitoring was entirely irrelevant in this regard.

The companies submitted that the wording used was not misleading and it would not lead clinicians into a false sense of security. The Cymbalta SPC did not mandate special monitoring even in patients with existing hypertension or cardiac disease. The statement in Section 4.4 of the SPC was that 'in patients with known hypertension and/or cardiac disease, blood pressure monitoring was recommended as appropriate'.

Lundbeck referred to the EPAR for Cymbalta. Page 31 referred to the data on blood pressure; however Lundbeck omitted the actual measured changes which could be seen to be small:

> 'Compared with placebo, duloxetine was associated with a significant difference in mean pulse (1.4bpm vs. –0.6bpm for placebo) and systolic BP (0.8mmHg vs. –1.4mm Hg for placebo). There was no significant difference in the incidence of sustained hypertension (sustained increases of either systolic or diastolic pressures) between the duloxetine-treated (1.3%) and placebo-treated (0.8%) groups in the placebo-controlled trials'.

Lundbeck also referred to the reported undertaking to provide CHMP with further data. The data requested had been submitted to the satisfaction of CHMP. The statement by Lundbeck that a future class effect warning to monitor blood pressure in all patients could not be excluded was speculative and inappropriate for a pharmaceutical company to make about a medicine.

In summary the companies rejected the allegation that the claim might endanger patient safety. The claim that 'No blood pressure monitoring is recommended in patients without pre-existing hypertension or cardiac disease' was appropriate considering clinicians' prior knowledge and expectation based upon the existing member of this class of medicine and was consistent with Section 4.4 of the SPC. The companies did not accept that they were in breach of Clauses 7.2 and 9.1.

PANEL RULING

The Panel noted the parties' submissions regarding differences between Cymbalta, Efexor and SSRIs and that Lilly and Boehringer Ingelheim wanted to differentiate Cymbalta from Efexor.

The relevant part of Section 4.4 of the Cymbalta SPC stated 'In patients with known hypertension and/or other cardiac disease, blood pressure, monitoring is recommended as appropriate'. On balance, the Panel considered that the claim 'No blood pressure monitoring is recommended in patients without pre-existing hypertension or cardiac disease' was not a fair reflection of the SPC statement and was confusing and ambiguous. The Panel ruled a breach of Clause 7.2 of the Code. The Panel considered that this ruling of a breach of Clause 7.2 encompassed consideration of the requirements of Clause 9.1. Nonetheless given that an allegation of a breach of this clause had been made it was obliged to rule upon it and a breach of Clause 9.1 was thus ruled.

Complaint received **15 March 2005**

Case completed **14 June 2005**

CASE AUTH/1695/3/05

HOSPITAL EMPLOYEE v ASTRAZENECA

Arrangements for meeting

A hospital employee complained anonymously about a meeting that an AstraZeneca representative had arranged for cardiologists. The complainant was concerned that the meeting had no educational content, and that the venue, a very prestigious and expensive (in excess of £200/per head) restaurant, was wholly unsuitable. The complainant further noted that the representative had asked a registrar to informally invite people on her behalf. The complainant alleged that such conduct was unprofessional.

The Panel noted that the meeting, over which the representative appeared to have little control, had been organised, from scratch, in less than three weeks. In early March prior to going on holiday the representative held preliminary discussions with a specialist registrar about the meeting and provisionally agreed that it be held at a restaurant suggested by the registrar. Intended invitees were discussed as was the purpose of the meeting ie to discuss proposals for a development workshop, topics covered at a course attended that day by the invitees and use of Crestor. On her return from holiday on a Friday and on learning that the registrar had issued invitations for the meeting on the following Monday, the representative, at very short notice, contacted the restaurant but discovered that it was fully booked. Arrangements were then made to go to another restaurant. It was unclear from AstraZeneca's submission whether the new venue was chosen by the representative or the registrar. No agenda, invitation or other materials were provided to attendees. The Panel noted that the representative had not wanted to let the invitees down and thus proceeded with the meeting even though according to AstraZeneca's submission she had not agreed the final date. The Panel considered, however, that the representative's first priority should have been to ensure that the meeting arrangements complied with the Code regardless of arrangements made by others. Responsibility for compliance with the Code could not be delegated to third parties.

The Panel noted that whilst the meeting was ultimately not held at the original restaurant there was, nonetheless, a provisional agreement that it would be the venue and verbal invitations were issued by the registrar on this basis. The Code referred to the offer of hospitality at meetings. Invitations to meetings were covered even if the meeting ultimately took place at a different venue. The Panel further noted that it had no way of knowing what the registrar had said about the proposed content of the meeting when issuing the verbal invitations.

The meeting itself was attended by a professor, four specialist registrars and the representative; took place in the public part of another, but similarly prestigious restaurant. There was no clear educational content; the discussion topics cited by AstraZeneca did not justify the provision of substantial hospitality. The informal nature of the arrangements including the verbal invitation and the absence of an agenda compounded the impression given of a mainly social evening with substantial hospitality.

The Panel considered that delegates would have been attracted by the venue rather than the content of the meeting and that the approximate cost of £66 per head was more than they would normally adopt if paying for themselves. The arrangements were wholly unacceptable in relation to the requirements of the Code and a breach was ruled.

The meeting had been arranged in apparent haste. The representative had provisionally agreed a venue without establishing its suitability. It was of concern that the representative did not realize until the Friday that the date of the following Monday was definite. The registrar had issued verbal invitations to the meeting. The venue was totally unacceptable, no agenda had been issued and there was no clear educational content. The Panel was extremely concerned about the informal, social nature of the arrangements. The representative had failed to maintain a high standard of ethical conduct and comply with all the relevant requirements of the Code. A breach was ruled.

The Panel was extremely concerned about the overall impression given by the arrangements. High standards had not been maintained. A breach of the Code was ruled. The absence of a clear educational content and the informal nature of the arrangements gave the impression that the meeting was primarily a social event at a prestigious restaurant; this was totally unacceptable and brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

A hospital employee complained anonymously about the arrangements for a meeting organised by a representative from AstraZeneca UK Limited.

COMPLAINT

The complainant was concerned that an AstraZeneca representative, had organised a meeting for 11 health professionals, primarily from a hospital cardiology team, at a named restaurant, on Monday, 21 March. She was concerned, firstly, that there was no educational content associated with the meeting; secondly that the restaurant was a very prestigious, expensive restaurant and thus wholly unsuitable. The complainant mentioned a cost in excess of £200 per head. Thirdly, the representative had asked a registrar to informally invite people on her behalf. The complainant alleged that such conduct was unprofessional.

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

RESPONSE

AstraZeneca confirmed that the representative had organized a meeting on the 21 March but it took place at a different restaurant to that named by the

complainant. The cost per head was £58 before discretionary service charge, including all food, beverages and VAT (the receipts were provided).

AstraZeneca explained that the representative had had preliminary discussions about the meeting with a specialist registrar who suggested the venue. The representative had heard of the restaurant but had not used it and did not know the average prices. The representative provisionally agreed to the venue with the intent of checking the restaurant on her return from holiday. When she telephoned the restaurant on her return, she was told there was no availability so she did not enquire as to the expected cost of the meal. If the representative had not been to a restaurant before, she would normally contact the restaurant and discuss the average price; if the cost was going to exceed the guidance within AstraZeneca policy she would not proceed with the booking.

AstraZeneca explained that the meeting that took place was organized for cardiology specialist registrars from two hospitals who had close working links particularly with work in outpatients clinics. An evening meeting was arranged as the invitees were attending an independent specialist registrar development workshop during the day.

A list of invitees and delegates was provided. These individuals were selected by the representative in conjunction with the specialist registrar from one of the hospitals who suggested suitable colleagues in line with the purpose of the meeting which was to discuss future initiatives for specialist registrars and, as they were cardiologists, to have some discussion relating to Crestor (rosuvastatin).

AstraZeneca submitted that the meeting had a clear educational content and although it took place in the main restaurant, the representative was satisfied that the tables were sufficiently far apart so that conversations of other diners could not be heard and vice versa and the proceedings were carried out in the manner of discreet discussion. No promotional materials were used. The key areas discussed were:

- Proposals for an AstraZeneca sponsored specialist registrar development workshop. The proposals were discussed and feedback obtained from these doctors as potential participants in the workshop
- Topics covered at an independent cardiology training day attended by the delegates that afternoon
- The use of Crestor in the two hospitals.

AstraZeneca submitted that the possibility of having a meeting with this group was first discussed in early March. The representative had made it clear in these preliminary discussions with the specialist registrar concerned that the purpose of the meeting was to discuss the topics above. Various dates were considered. No agenda, invitation or other materials were provided to the attendees. As she was about to go on holiday, the representative agreed the preliminary arrangements and intended invitees for the meeting with the specialist registrar. On her return from holiday on a Friday she was informed by the specialist registrar that he had invited some of the intended delegates for the following Monday evening. Until this point, the representative had not realised that the date was definitely set but decided to proceed with the meeting as she did not want to let the invitees down at such short notice.

AstraZeneca stated that it took adherence to the Code very seriously and that although the main allegations in the complaint were largely unfounded, some of the meeting arrangements were unsatisfactory. The representative should have exerted more control over the arrangements. It would have been good practice to ensure there was a written agenda and invitation issued from AstraZeneca. AstraZeneca was satisfied that the public were not exposed to the promotion of prescription-only medicines, however it considered that more care should have been taken with the restaurant seating arrangements.

AstraZeneca submitted that it had a rigorous approach to corporate governance and the Code and as company guidelines and expectations were not followed, the representative and her manager had been reprimanded. Both would undergo some additional training and education on the Code to help them understand best practice for future meetings. Guidance and learning would also be shared with all relevant personnel within the company.

AstraZeneca noted that as the representative was not as rigorous in setting up this meeting as it required, it accepted there had been a breach of Clause 15.2 of the Code but denied breaches of Clauses 19.1, 9.1 and 2.

PANEL RULING

The Panel noted that Clause 19.1 of the Code permitted companies to provide appropriate hospitality to members of the health professions and appropriate administrative staff in association with scientific and promotional meetings, scientific congresses and other such meetings. Hospitality must be secondary to the purpose of the meeting and the level of hospitality offered must be appropriate and not out of proportion to the occasion. The costs involved should not exceed those which participants might normally pay when paying for themselves. The supplementary information to Clause 19.1 stated that meetings should have a clear educational content and it should be the programme that attracted delegates and not the associated hospitality or venue. The impression created by the arrangements was an important factor. Meetings organised for health professionals and/or administrative staff which were wholly or mainly of a sporting or social nature were unacceptable.

The Panel did not accept AstraZeneca's submission that there was no specific complaint about what happened at the actual meeting. The complainant had, *inter alia*, alleged that there was no educational content associated with the meeting and had referred to the level of hospitality thus requiring an examination of what actually took place. That the meeting ultimately took place at a venue different to that stated by the complainant was irrelevant.

The Panel noted that the meeting, over which the representative appeared to have little control, had been organised, from scratch, in less than three weeks.

In early March prior to going on holiday the representative held preliminary discussions with a specialist registrar about the meeting and provisionally agreed that it be held at the restaurant suggested by the registrar. Intended invitees were discussed as was the purpose of the meeting namely to discuss proposals for a development workshop, topics covered at a course attended that day by the invitees and use of Crestor. On her return from holiday on the Friday and on learning that the registrar had issued invitations for the meeting on the following Monday, the representative, at very short notice, contacted the restaurant but discovered that it was fully booked. Arrangements were then made for the meeting to be held at an alternative restaurant. It was unclear from AstraZeneca's submission whether the new venue was chosen by the representative or the registrar. No agenda, invitation or other materials were provided to attendees. The Panel noted that the representative had not wanted to let the invitees down and thus proceeded with the meeting even though according to AstraZeneca's submission she had not agreed the final date. The Panel considered, however, that the representative's first priority should have been to ensure that the meeting arrangements complied with the Code regardless of arrangements made by others. Responsibility for compliance with the Code could not be delegated to third parties.

Whilst the Panel noted AstraZeneca's submission regarding the planned discussions, it nonetheless considered that the educational content was minimal and the offer and provision of dinner at a restaurant in association with such a meeting was disproportionate and unacceptable in relation to the requirements of Clause 19.1.

The Panel noted that whilst the meeting was ultimately not held at the restaurant identified by the complainant there was, nonetheless, a provisional agreement that it would be the venue and verbal invitations were issued by the registrar on this basis. The Code referred to the offer of hospitality at meetings. Invitations to meetings were covered even if the meeting ultimately took place at a different venue.

The Panel noted that the first choice restaurant was prestigious with one Mitchelin star. The Panel was extremely concerned that the representative had provisionally agreed such a venue before establishing its suitability. Verbal invitations had been issued by the registrar. The Panel noted AstraZeneca's submission about the content of the meeting and that the purpose of the meeting had been made clear during preliminary discussions with the registrar but it had no way of knowing what the registrar had said about the proposed content of the meeting or on what basis the verbal invitations had been issued.

The Panel noted that the actual meeting attended by a professor, four specialist registrars and the representative took place in the public part of another, equally prestigious, restaurant (which also held one Mitchelin star). There was no clear educational content; the discussion topics cited by AstraZeneca did not justify the provision of substantial hospitality. The informal nature of the arrangements including the verbal invitation and the absence of an agenda compounded the impression given of a mainly social evening with substantial hospitality. The Panel considered that delegates would have been attracted by the venue rather than the content of the meeting. The Panel considered that the approximate cost of £66 per head was more than recipients would normally adopt if paying for themselves. The arrangements were wholly unacceptable in relation to the requirements of Clause 19.1 and a breach of that clause was ruled.

The Panel was extremely concerned about the conduct of the representative. The Panel noted AstraZeneca's submission that the company's guidelines had not been followed by the representative and her manager. The Panel noted that, nonetheless, Clause 15.10 provided that companies were responsible for the activities of their representatives if these were within the scope of their employment even if contrary to instructions given.

The meeting had been arranged in apparent haste. The representative had provisionally agreed the first venue without establishing its suitability. It was of concern that the representative did not realize until her return from holiday that the date for the meeting was definite. It was beholden upon representatives to be abundantly clear when making arrangements for meetings. It appeared that the registrar had the impression that the date was acceptable and had invited people on this basis. The venue was totally unacceptable. No written invitations or agenda had been issued. There was no clear educational content. The Panel was extremely concerned about the informal, social nature of the arrangements. The representative had failed to maintain a high standard of ethical conduct; she had not complied with all the relevant requirements of the Code. A breach of Clause 15.2 was ruled.

The Panel was extremely concerned about the overall impression given by the arrangements. High standards had not been maintained. A breach of Clause 9.1 was ruled. The absence of a clear educational content and the informal nature of the arrangements gave the impression that the meeting was primarily a social event at a prestigious restaurant. This was the impression given to the complainant. The arrangements and impression given were totally unacceptable and brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

* * * * *

During its consideration of this case the Panel was concerned to note that Internet reviews of the restaurant where the meeting was held referred to tables being cramped and the background noise so loud that conversation was almost impossible. These descriptions were at odds with the representative's description of the venue. It requested that AstraZeneca be advised of its concerns about this discrepancy.

Complaint received **21 March 2005**

Case completed **11 May 2005**

CASE AUTH/1696/3/05 *NO BREACH OF THE CODE*

BRISTOL-MYERS SQUIBB v BOEHRINGER INGELHEIM

Abstract review

Bristol-Myers Squibb complained about a booklet, supported by an unrestricted medical grant from Boehringer Ingelheim, which contained a review of selected abstracts from conferences relating to protease inhibitors. Information on Boehringer Ingelheim's unlicensed product, tipranavir, was included. The inside front cover stated that the abstract review was an independent professional news service provided by a medical intelligence agency.

Bristol-Myers Squibb stated that the abstract review had been sent unsolicited to health professionals; although balanced and scientific it could not be regarded as the legitimate exchange of scientific information as without Boehringer Ingelheim's involvement it would not have been published. It was unlikely that Boehringer Ingelheim had sponsored the review without having any idea of its content. Bristol-Myers Squibb alleged that the review was disguised promotion and promoted an unlicensed medicine.

The Panel noted that the abstract review had been supported by an educational grant from Boehringer Ingelheim as acknowledged on the document itself. The review had been initiated by the medical intelligence agency which had identified critical issues in HIV treatment, and then asked Boehringer Ingelheim and other companies for an educational grant to finance the publication. The selection of topics and content of the review was the responsibility of the agency in association with a guest editor. Boehringer Ingelheim had had no direct influence on the content, other than to review its medical accuracy, and no direct influence as to who should receive the review although it had agreed to the quantity to be mailed. The guest editor had had no contact with anyone from Boehringer Ingelheim. The review had not been used by Boehringer Ingelheim for promotional purposes.

Emails between Boehringer Ingelheim and the agency referred to supporting the company's objectives with tripanavir and Viramune (nevirapine). What appeared to be the guest editor's brief stated that 'In addition to subsidising the production of a text that honestly and usefully reports the latest news on the Sponsor's products, the Sponsor expects to see negative as well as positive information reported concerning its products'. The Panel considered that Boehringer Ingelheim would thus have expected some information on its products to appear in the abstract review in return for its sponsorship.

The Panel considered that although Boehringer Ingelheim had sponsored the abstract review in the almost certain knowledge that information on tipranavir would be included, it had not been able to influence the content of the publication in a manner favourable to its own interests. On balance the Panel considered that there had been an arm's length arrangement between Boehringer Ingelheim and the medical intelligence agency with regard to the generation, content and distribution of the abstract review. The guest editor had had no contact with Boehringer Ingelheim and the company had not used the review for a promotional purpose. The Panel considered that Boehringer Ingelheim was thus not liable under the Code for the content of the abstract review. No breach of the Code was ruled.

Bristol-Myers Squibb Pharmaceuticals Limited complained about a 28 page publication entitled 'Current Research and Expert Commentary, Protease Inhibitor Therapy In The Treatment-Experienced Patient' which contained a review of selected abstracts from conferences relating to protease inhibitors and was supported by an educational grant from Boehringer Ingelheim Limited. The inside front cover stated that the abstract review was an independent professional news service provided by a medical intelligence agency. Intercompany correspondence had failed to resolve the matter.

COMPLAINT

Bristol-Myers Squibb stated that the abstract review had been sent, unsolicited, to an unknown distribution of health professionals. Although the publication was apparently sponsored through an unrestricted educational grant, it had clearly been commissioned by Boehringer Ingelheim. The only interest the company had in protease inhibitors was tipranavir, currently in development and available on a named patient basis in the UK.

Bristol-Myers Squibb did not refute that the review was balanced and scientific, however it could not be regarded as the legitimate exchange of scientific information, as, without sponsorship from Boehringer Ingelheim, this communication would not have occurred. It was also sent unsolicited to an unknown number of health professionals, containing information on Boehringer Ingelheim's unlicensed product. It was unlikely that Boehringer Ingelheim would have sponsored a publication without having any idea of its content.

Bristol-Myers Squibb stated that the review was not consistent with other 'plain paper' patient or advocacy group publications in the HIV field. It was of high quality, heavy weight paper, although an attempt had been made to make it appear bland in nature.

Bristol-Myers Squibb alleged that the abstract review breached Clauses 3.1 and 10.1 of the Code.

RESPONSE

Boehringer Ingelheim submitted that the medical intelligence agency was an independent agency that monitored various medical meetings and produced reports on them for health professionals. In order to select the contents of such reviews, the agency analysed its database to assess critical clinical issues facing clinicians in the concerned area of therapy. In this instance, the agency had identified that potency and resistance to therapy were critical issues in the management of treatment-experienced HIV infected patients. The agency then asked Boehringer

Ingelheim for an educational grant to finance the generation of such an abstract review following the 7th International Congress in Drug Therapy in HIV Infection which took place in Glasgow, 14-18 November 2004. This grant was provided by Boehringer Ingelheim, with the understanding that it would have no influence over the content (other than a clinical review of medical accuracy) or the distribution of the publication.

In addition, Boehringer Ingelheim submitted that a consultant physician in HIV medicine was asked to be the guest editor for the abstract review, and at his suggestion, the agency incorporated abstracts from the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy held in Washington, 29 October to 2 November 2004. The guest editor then reviewed a list of abstracts from the two meetings supplied by the agency, selected eighteen and compiled a guest editorial to the abstract review. Thus the selection of topics and content of the report was the responsibility and sole decision of the agency in consultation with the guest editor, and this was stated quite clearly on the cover of the report (front and back) as well as on the inside of the front and back covers.

Boehringer Ingelheim confirmed that the abstract review was mailed by the agency to consultants in genitourinary medicine, infectious diseases and HIV; HIV pharmacists were also included in the distribution. Boehringer Ingelheim had no influence on this audience, which was selected by the agency from a mailing list purchased by it from an independent specialist mailing company.

Boehringer Ingelheim acknowledged that it supported the production of this review by means of an unconditional educational grant, as clearly stated on the front cover, and that it had a current commercial interest in this area with Viramune and a future anticipated availability of tipranavir. However, this abstract review constituted legitimate exchange of medical and scientific information, consistent with the supplementary information to Clause 3 of the Code.

As noted by Bristol-Myers Squibb, the report was balanced and scientific; of the abstracts where specific products were mentioned, seven discussed lopinavir (Abbott), nine discussed atazanavir (Bristol-Myers Squibb) and only two mentioned tipranavir. Boehringer Ingelheim disagreed with the assertion that this was not legitimate exchange of information. Boehringer Ingelheim was not aware of any other single publication reviewing the abstracts from these two conferences on this specific topic. Therefore, this review provided up-to-date information for clinicians unable to attend both conferences.

Boehringer Ingelheim submitted that as the abstract review was an independent publication by the agency, the physical format was not within the control of Boehringer Ingelheim. The publication was a professional review for health professionals and was not intended as a patient or advocacy group publication, as suggested by Bristol-Myers Squibb.

Boehringer Ingelheim noted that the Code did not prohibit the exchange of medical and scientific information during the development of a medicine (referred to in the supplementary information to Clause 3). The exchange of medical and scientific information did not constitute promotion and therefore could not be considered in breach of Clauses 10.1 or 3.1 of the Code.

In Boehringer Ingelheim's view the abstract review was an independent, non-promotional review of scientific data presented at recent international conferences which it had supported by an educational grant. Boehringer Ingelheim, denied breaches of Clauses 10.1 and Clause 3.1 of the Code.

In response to a request for further information, Boehringer Ingelheim stated that the major differences with regard to giving a grant to the agency or employing a public relations (PR) agency for the same purpose, related to the fact that a PR agency would be provided with a full marketing brief to work from, in order to disseminate a promotional message to a specific, targeted audience of Boehringer Ingelheim's choosing. Furthermore, Boehringer Ingelheim, not the guest editor, would also have full, final sign off.

Boehringer Ingelheim stated that the publication at issue would not exist in the absence of sponsorship by a pharmaceutical company; however, several pharmaceutical companies were approached without favour by the agency for sponsorship of the abstract review.

Boehringer Ingelheim confirmed that it had not influenced the distribution of the abstract review. Other than the mailing at issue by the agency, this publication had not been distributed in any other form, nor had it been used or referred to by any Boehringer Ingelheim representative or on any Boehringer Ingelheim exhibition stand.

PANEL RULING

The Panel noted that it was acceptable for companies to sponsor material. It had previously been decided 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 abstract review in question had been supported by an educational grant from Boehringer Ingelheim Limited as acknowledged on the document itself. The review had been initiated by the medical intelligence agency which had identified critical issues faced by clinicians treating HIV patients. The agency had approached Boehringer Ingelheim and other companies to request an educational grant to finance the abstract review. The selection of topics and content of the review was the responsibility of the agency in association with a guest editor. Boehringer Ingelheim had had no direct influence on the content of the review, other than a clinical review of its

medical accuracy. Although Boehringer Ingelheim had similarly had no direct influence as to who should receive the review it had agreed to the quantity to be mailed. The guest editor had had no contact with anyone from Boehringer Ingelheim. The review had not been used by Boehringer Ingelheim for promotional purposes – it had only been mailed by the agency to health professionals.

The Panel noted the content of emails sent between Boehringer Ingelheim and the agency when the two were discussing potential sponsorship of the abstract review. Reference was made by the agency to 'educational clinical communications to support your objectives with Viramune and Tipranavir' and by Boehringer Ingelheim to 'abstract books etc for both Viramune and Tipranavir'. A copy of the brief, which appeared to have been given to the guest editor, was provided. The brief stated that 'In addition to subsidising the production of a text that honestly and usefully reports the latest news on the Sponsor's products, the Sponsor expects to see negative as well as positive information reported concerning its products'. The Panel considered that Boehringer Ingelheim would thus have expected some information on its products to appear in the abstract review in return for its sponsorship. The brief further stated that 'The Sponsor also expects to see relevant news concerning other therapies of interest that clinicians might be expected to consider using to enhance the well-being of their patients instead of or in addition to the Sponsor's products'.

The Panel considered that how a document such as the abstract review would be viewed under the Code would depend upon the arrangements between the parties and the final use of the document.

The Panel considered that although Boehringer Ingelheim had sponsored the abstract review in the almost certain knowledge that information on tipranavir would be included, it had not been able to influence the content of the publication in a manner favourable to its own interests. On balance the Panel considered that there had been an arm's length arrangement between Boehringer Ingelheim and the medical intelligence agency with regard to the generation, content and distribution of the abstract review. The guest editor had had no contact with Boehringer Ingelheim and the company had not used the review for a promotional purpose. The Panel considered that Boehringer Ingelheim was thus not liable under the Code for the content of the abstract review. No breaches of Clauses 3.1 and 10.1 of the Code were ruled.

Complaint received **22 March 2005**

Case completed **7 June 2005**

CASE AUTH/1698/3/05

SANOFI-AVENTIS v NOVO NORDISK

NovoMix 30 journal advertisement

Sanofi-Aventis complained about a journal advertisement for NovoMix 30 FlexPen (biphasic insulin aspart) produced by Novo Nordisk. NovoMix 30 was indicated, *inter alia*, for the treatment of type 2 diabetes either as monotherapy or in combination with metformin. Sanofi-Aventis supplied Lantus (insulin glargine). The only claim in the advertisement, 'In type 2 diabetes 60% more people reached HbA_{1c} target of < 7% with twice daily NovoMix 30 compared to insulin glargine', was referenced to data on file.

Sanofi-Aventis noted that no details of the study from which the claim was derived were given eg how long the study lasted or what concomitant medicines were used. Without such information it was impossible for a health professional to interpret the claim. It was therefore misleading from the outset.

Moreover, the heading 'In type 2 diabetes' suggested that this claim was made for all type 2 diabetics. However the claim was based on data derived from a subgroup analysis of one study of insulin naïve patients with inadequate glycaemic control on oral therapy. All patients in the subgroup analysis continued taking metformin as their sole oral antidiabetic medication to which was added either NovoMix 30 (n=72) or Lantus (n=76). Type 2 diabetics, however, formed a broad spectrum with respect to their stage of diabetes and thus the medical management required. The patients in the study were one particular group from this spectrum treated with one of two very specific regimens. To make a broad claim 'In type 2 diabetes' was alleged to be misleading and exaggerated.

Furthermore it was inappropriate to consider HbA_{1c} changes in isolation. Treatment with insulin constituted a fine balance of improving glycaemic control whilst minimising hypoglycaemia and weight gain. No mention was made in the advertisement that in the full study cohort (data for the subgroup analysis was not available), the overall rate of hypoglycaemia (documented plasma glucose of < 56mg/d) was significantly greater with NovoMix 30 compared with Lantus (3.4 v 0.7 episodes/patient year, $p < 0.05$) with 43% and 16% of subjects respectively reporting hypoglycaemic episodes. Nor was any mention made of the greater weight gain with NovoMix 30 (5.6 v 3kg, $p< 0.01$). The claim was therefore alleged to be misleading by omission.

The Panel noted that the claim '60% more people reached HbA_{1c} target of <7% with twice daily NovoMix 30 compared with insulin glargine' was very specific. The data on file to support the claim related to a very specific group of type 2 diabetics, insulin naïve patients who had insulin added to their metformin therapy because they were inadequately controlled on optimal doses of metformin alone. The Panel was concerned that the claim was based on a subgroup analysis. The Panel noted that although doctors would be very familiar with the usual practice of adding in insulin therapy when a type 2 diabetic did not achieve adequate blood glucose control on oral therapy alone, NovoMix 30 could be used as monotherapy in type 2 diabetes. The Panel considered that without information about the use of concomitant medication and the type 2 diabetics to whom the values quoted applied, health professionals would be unable to judge the clinical significance of the claim. The Panel considered that the claim was misleading in that regard and ruled a breach of the Code which was upheld on appeal by Novo Nordisk. The Panel further considered that the implication that the claim applied to all type 2 diabetics was exaggerated as alleged. A breach of the Code was ruled which was also upheld on appeal by Novo Nordisk.

The Panel noted that the advertisement in question dealt only with one aspect of diabetic control. There was, however, no implication that achievement of HbA_{1c} targets was all that needed to be considered in treating patients. In that regard the Panel did not consider that omission of data regarding weight gain or hypoglycaemia was misleading. No breach of the Code was ruled.

Sanofi-Aventis complained about a journal advertisement (ref NM/146/1104) for NovoMix 30 FlexPen (biphasic insulin aspart) produced by Novo Nordisk Limited. NovoMix 30 was indicated for the treatment of diabetes mellitus. In type 2 diabetes it could be given as monotherapy or in combination with metformin. Inter-company correspondence had not resolved the matter. Sanofi-Aventis supplied Lantus (insulin glargine).

Claim 'In type 2 diabetes 60% more people reached HbA_{1c} target of < 7% with twice daily NovoMix 30 compared to insulin glargine'.

The claim was referenced to data on file and was the only one to appear in the advertisement.

COMPLAINT

Sanofi-Aventis noted that no details of the study from which the claim was derived were given. For example, there was no information about how long the study lasted or what concomitant medicines were used. Without such information it was impossible for a health professional to interpret the claim. It was therefore misleading from the outset.

Moreover, the heading 'In type 2 diabetes' suggested that this claim was made for all type 2 diabetics. However the data on file on which the claim was based, showed that this could not be the case. The claim was based on data derived from a subgroup analysis of a single study. Subjects enrolled in the main study were insulin naïve and had inadequate glycaemic control on oral antidiabetic medicines. The subgroup in question consisted of 72 patients taking NovoMix 30 and 76 taking Lantus, all patients in the subgroup analysis continued taking metformin as their sole oral antidiabetic medication.

Type 2 diabetics formed a broad spectrum with respect to their stage of diabetes and the medical management that was consequently required. For

example, patients ranged from those who had just been diagnosed and required improved diet and augmented exercise alone to control their blood sugar, through to those who required four or more injections of insulin per day in conjunction with a number of oral antidiabetic medicines. The patients included in this study were one particular group from this spectrum and were treated with one of two very specific regimens. To make a broad claim 'In type 2 diabetes' was misleading and exaggerated.

Furthermore, as Novo Nordisk noted in a recent appeal, it was inappropriate to consider HbA_{1c} changes in isolation. Management of patients with insulin constituted a fine balance of improving glycaemic control whilst minimising hypoglycaemia and weight gain. No mention was made in the advertisement that in the full study cohort (data for the subgroup analysis was not available), the overall rate of hypoglycaemia (documented plasma glucose of < 56mg/d) was significantly greater in the group treated with NovoMix 30 compared to those treated with Lantus (3.4 v 0.7 episodes per patient year, $p<0.05$) with 43% and 16% of subjects in the respective groups reporting hypoglycaemic episodes. In addition no mention was made of the greater weight gain in the NovoMix 30 group (5.6 v 3kg, $p< 0.01$). The claim was therefore misleading by omission in both these regards.

Sanofi-Aventis alleged that the advertisement was misleading and exaggerated in breach of Clauses 7.3 and 7.10 of the Code.

RESPONSE

Novo Nordisk noted that the claim at issue was referenced to Novo Nordisk data on file 2163, a subgroup analysis of the patients in the INITIATE study who were not taking thiazolidinediones (TZD). In this 28 week study, 233 insulin naïve patients, inadequately controlled on oral medicine, were randomised into two groups. One group received NovoMix 30 twice daily and the other Lantus, once daily. All patients were taking metformin and some patients in both groups were also taking thiazolidinediones (TZDs). All other antidiabetic medicines were stopped. The doses of both insulins were increased according to an algorithm directed forced titration based on their blood glucose levels. The study compared the efficacy and safety of both treatment options by looking at HbA_{1c} levels and secondary endpoints, such as the rate of hypoglycaemic events.

As the patients in the INITIATE study were stratified according to TZD use, Novo Nordisk looked at the 148 patients at the end of study not taking TZD as this was contraindicated with insulin use in the UK. Forty-seven of the 72 (65.3%) patients in the NovoMix 30 arm reached the target HbA_{1c} of < 7% as suggested by the American Diabetes Association. Thirty-one (40.8%) of the 76 patients in the Lantus arm reached the same target. Simple calculations led Novo Nordisk to the claim that 65.3% was 60% more than 40.8%, hence the claim that 60% more people reached their target of 7%.

With regard to hypoglycaemia Novo Nordisk noted that this was a well recognised adverse effect of intensive insulin therapy according to the Diabetes Control and Complications Trial. The closer a patient's HbA_{1c} was to normal, and the tighter their blood glucose control, the more likely he or she was to experience a hypoglycaemic event.

In the 28 week trial and in the whole study group (there was no subgroup analysis of hypoglycaemia), 43% of the patients in the NovoMix 30 group had confirmed minor hypoglycaemic events (a blood glucose reading of < 56mg/dl (3,11mmol/l) with or without symptoms that did not require help from a third party) compared to 16% of patients in the Lantus group. One patient in the Lantus group had a major hypoglycaemic event.

The median rate of minor hypoglycaemia calculated for the patients that had minor hypoglycaemic events, was 0.3 episodes/patient month for the NovoMix 30 group and 0.2 for patients in the Lantus group (p=ns). It was notable that the greater rate of hypoglycaemia for the NovoMix 30 group compared with the Lantus group did not deter patients from achieving improved glycaemic control and no one withdrew from the study because they found this rate unacceptably high. The Insulin Treatment Satisfaction Questionnaire completed at the end of the study showed no significant difference on Quality of Life perceived between patients in the two arms of the study.

Patients in the NovoMix 30 arm had a higher rate of minor hypoglycaemic events because their control was better; the average HbA_{1c} was 0.5% lower than in the Lantus arm.

Most clinicians saw minor hypoglycaemic events as an unfortunate complication of tight control that did not have an impact on mortality or morbidity. What was important was the rate of possible life threatening major hypoglycaemic events which did have a major impact on a patient's life. There was no significant difference in that between the two arms of the trial.

Novo Nordisk noted that weight gain was proportional to the amount of insulin received. In this study, and again in the whole study group, patients on NovoMix 30 gained more weight than those on Lantus. If this was adjusted to the average amount of insulin received, there was no statistical difference. At the end of the study, the amount of insulin the patients in the NovoMix 30 arm received was 0.82U/kg and 0.5U/kg in the Lantus arm. As the NovoMix 30 patients received more insulin and had better control, they were bound to gain more weight. Again, this was an unfortunate complication of tight control.

Novo Nordisk noted that type 2 diabetes was treated in a stepwise fashion similar to the approach taken in the treatment of asthma or hypertension. Initially type 2 diabetics would be treated with lifestyle modifications – diet, exercise and weight loss as well as limiting the other risk factors for cardiovascular disease such as smoking, hypertension and hypercholesterolaemia. Oral medicines lowered the insulin resistance, enhanced glucose metabolism and stimulated insulin secretion and would be the next line of treatment, should lifestyle modifications not keep a patient's blood glucose levels under an accepted level.

The National Institute for Clinical Excellence (NICE) clinical guideline published in September 2002 on the treatment of type 2 diabetes stated that an HbA_{1c} target between 6.5% and 7.5% should be set for each patient, based on their risk profile. The American Diabetes Association recommended an HbA_{1c} of <7%. In subsection 3.11 of the NICE guideline it was stated that 'insulin therapy should be offered to people with diabetes with inadequate blood glucose control on optimised oral glucose lowering drugs'.

Based on these recommendations, most clinicians would consider starting insulin treatment when a patient's HbA_{1c} and blood glucose levels deteriorated. The evidence that a lower HbA_{1c} level could prevent micro- and macro-vascular complications in diabetics and lower morbidity and mortality later in life, was now overwhelming (UK Prospective Diabetes Study). This would be the third and final level of treatment that would follow on lifestyle modifications and oral medicine. Insulin therapy was the last step. As the disease progressed, clinicians would change the way the insulin was administrated by changing the dosage, the type of insulin and the amount of injections per day.

At present once a day long acting insulin or twice a day premix was the most popular choice to start insulin therapy in the UK and US. Dailey (2004) stated 'In (some) patients with … late stage T2DM, basal insulin can be supplemented with a mealtime bolus of human rapid-acting insulin to produce a more physiologic type of glycemic control'. NovoMix30 attempted to marry this need for a long acting and short acting insulin in a premixed preparation that could be given once, twice or three times daily with meals. This supplemented a patient's basal requirement as well as addressing postprandial needs.

The INITIATE study found that patients with a higher HbA_{1c} did better in the NovoMix 30 arm than the Lantus arm. The HbA_{1c} reduction was larger for patients whose baseline HbA_{1c} values were >8.5% in the NovoMix 30 arm than in the Lantus arm. This difference was less pronounced in the patients with a lower HbA_{1c} at the start of trial. This suggested that the mixture of short and long acting insulin would be more effective later in the disease than only administering a long acting insulin.

Novo Nordisk noted that Sanofi-Aventis had complained that lack of information in the advertisement regarding the duration of the study or concomitant medicines taken by the patients was misleading. Novo Nordisk failed to see how that would be problematic as both arms of the study were taking part for exactly the same length of time and were on exactly the same medication, except for the two insulins under investigation.

Novo Nordisk noted that Sanofi-Aventis had also complained that the phrase 'In type 2 diabetes' was exaggerated and misleading as it could be seen to refer to the whole spectrum of type 2 diabetics from those in the early stages with lifestyle modifications only, to later when they needed oral medicines and then finally when they needed insulin.

Novo Nordisk believed any health professional reading the words 'insulin' and 'type 2 diabetes' in one sentence, would know exactly to what type of patients it was referring. 'Type 2' was added so as not to confuse readers with type 1 diabetes patients who also needed insulin but on a completely different regimen for a completely different pathology.

There were quite clear guidelines on when insulin should be initiated in type 2 diabetes and when it was relevant to consider insulin. Health professionals had enough experience and guidelines to know at what stage insulin treatment was appropriate.

The advertisement in question set out to highlight the difference between two treatment options when a clinician needed to start a patient on insulin and also looking further ahead as the patient continued to use insulin for the rest of his life.

Novo Nordisk noted that Sanofi-Aventis had further alleged that the advertisement was misleading as it did not mention the study results regarding weight or hypoglycaemia. Diabetes management was indeed more than just an HbA_{1c}. It was about prolonging life, preventing complications and improving quality of life for all patients. HbA_{1c}, however, was the most reliable indicator of metabolic control at present and was the single most important factor in predicting morbidity and mortality. It was used as the indicator of how well a patient was treated. It was mentioned in all guidelines, government targets, assessment of GP practices and clinics and most importantly given to a patient as a benchmark to see how well he or she was doing. As mentioned above, with tightened control, patients tended to gain weight and their risk of hypoglycaemia went higher. These were important factors, as were their cholesterol count, blood pressure, amount they smoked, psychological acceptance of their disease and management.

Novo Nordisk did not agree that focussing on the single most important indicator of a patient's diabetes control in a short advertisement and not mentioning the other secondary factors, was misleading. Meeting the target of HbA_{1c} of < 7% was the most important message Novo Nordisk could convey. All diabetes treatments aimed to lower HbA_{1c} levels and meet set targets. The number of hypoglycaemic attacks and the amount of weight gained were not mentioned in any present guidelines as important factors in choosing between NovoMix30 or Lantus. They were actually not related to the kind of insulin a patient was receiving as much as the amount received and how tight control was. It was irrelevant in the choice between Lantus and NovoMix30.

Novo Nordisk denied all alleged breaches of the Code. With regard to Clause 7.3, it had explained in detail why it did not believe the advertisement was misleading. Novo Nordisk considered the mention of duration of the trial and use of other oral medicines was irrelevant as omitting this could not unfairly bias one arm of the trial against the other. 'In type 2 diabetes' was included in the advertisement to avoid confusion with type 1 patients and in conjunction with the word 'insulin' later in the sentence should be clear enough to any clinician.

Weight gain and hypoglycaemic events were separate indicators to reaching an HbA_{1c} target of 7% and omitting them in this short advertisement was

irrelevant. Novo Nordisk did not consider this advertisement was misleading for these reasons.

This was a comparison between two medicines intended for the same purpose. One relevant, substantiable and representative feature was compared. No confusion was created between the medicine advertised and the competitor. No trade marks, trade names or other distinguishing marks were discredited or denigrated. No unfair disadvantage was taken of the reputation of a trade mark or trade name and nothing was presented as an imitation or replica. Novo Nordisk did not consider the advertisement to be in breach of Clause 7.3.

Novo Nordisk submitted that it did not exaggerate, use any embracing claim or superlatives and did not state that its medicine had some special merit, quality or property that was not substantiated in the INITIATE study. Novo Nordisk thus denied a breach of Clause 7.10.

PANEL RULING

The Panel noted that the claim '60% more people reached HbA_{1c} target of <7% with twice daily NovoMix 30 compared with insulin glargine' was a very specific claim. The data on file used to support the claim related to a very specific group of type 2 diabetics, insulin naïve patients who had insulin added to their metformin therapy because they were inadequately controlled on optimal doses of metformin alone. The Panel was concerned that the claim was based on a subgroup analysis of 148 patients in the INITIATE study. The Panel noted that although doctors would be very familiar with the usual practice of adding in insulin therapy when a type 2 diabetic did not achieve adequate blood glucose control on oral therapy alone, NovoMix 30 could be used as monotherapy in type 2 diabetes. The Panel considered that without information about the use of concomitant medication and the type 2 diabetics to whom the values quoted applied, health professionals would be unable to judge the clinical significance of the claim. The Panel considered that the claim was misleading in that regard and ruled a breach of Clause 7.3. The Panel further considered that the implication that the claim applied to all type 2 diabetics was exaggerated as alleged. A breach of Clause 7.10 was ruled.

The Panel noted that the advertisement dealt only with one aspect of diabetic control. There was, however, no implication that achievement of HbA_{1c} targets was all that needed to be considered in treating patients. In that regard the Panel did not consider that omission of data regarding weight gain or hypoglycaemia was misleading. No breach of Clause 7.3 was ruled.

APPEAL BY NOVO NORDISK

Novo Nordisk noted the Panel's concern that the claim was based on a subgroup analysis of the INITIATE study of 148 patients. This study was a 28-week trial on type 2 diabetics that were taking metformin with other oral agents and had an HbA_{1c} of >8%, implying failure on oral therapy. If the patients were taking secretagogues or alpha-glucosidase inhibitors, they were stopped. Metformin was continued in all patients and any patients taking TZDs were continued on them. Patients were then randomised to either receive Lantus once a day or NovoMix30 twice daily, based on titration guidelines.

Novo Nordisk submitted that because concomitant use of TZDs and insulin was contraindicated in Europe, a subgroup analysis was done on the 148 patients not taking them. This analysis would be published as a paper and the results were presently available upon request. The results of the HbA_{1c} values for the patients in this subgroup analysis were very similar to those for the whole group. A study of 148 patients was large enough to highlight this difference with confidence.

Novo Nordisk noted that type 2 diabetes was a progressive disease with increasing insulin resistance and a decrease in insulin production by the pancreas over many years. Type 2 diabetics were treated in a stepwise manner in a very similar way to patients with asthma or hypertension; one treatment would be started and if that was not adequate the next would be added according to internationally accepted guidelines. Type 2 diabetics were initially treated with lifestyle modifications. When that failed oral medicines would be added to lower insulin resistance, enhance glucose metabolism and stimulate insulin secretion. Step 3 would be to add insulin when pancreatic production of insulin was no longer adequate.

Novo Nordisk noted that clinical guidance from NICE, published in September 2002 on the treatment of type 2 diabetes stated that an HbA_{1c} target of 6.5-7.5% should be set for each patient, based on their risk profile. The American Diabetes Association recommended an HbA_{1c} target of <7% and the International Diabetes Federation and the American College of Clinical Endocrinologists both recommended a target of 6.5%. Subsection 3.11 of the NICE guidance stated 'insulin therapy should be offered to people with diabetes with inadequate blood glucose control on optimised oral glucose lowering drugs'. Based on these recommendations, most clinicians would look at a patient's HbA_{1c} and blood glucose levels and consider starting insulin treatment when they deteriorated. This would be the third level of treatment that would follow lifestyle modifications and oral medication.

Novo Nordisk submitted that in keeping with a stepwise approach, oral therapy in the form of insulin sensitizers would be continued. Raskin (2005) stated 'the only really effective approach is to use insulin/insulin sensitizer combination therapy' and cited three studies to support this statement. It was only when metformin was contraindicated that type 2 diabetics on insulin would not be using metformin as well. This had become standard practice in the UK.

Novo Nordisk noted that there was no 'fourth level of treatment' in this stepwise approach, where other medicines got added on. Adding insulin therapy was the last step. As the disease progressed clinicians would change the dosage, frequency or type of insulin. Therefore, it was not misleading not to state

that metformin was included in both arms of the study. Had metformin not been included Novo Nordisk agreed that this would have been worthy of comment.

Novo Nordisk noted that as stated above, very clear guidelines were in place as to when insulin should be started. The choice of which insulin to start and continue with was still controversial. At present once daily long acting insulin or twice daily premix was the most popular choice to start insulin therapy in the UK and US. According to its SPC Lantus was indicated for once daily subcutaneous administration for the treatment of adult, adolescents and children over the age of 6 with diabetes mellitus.

Novo Nordisk noted Dailey (2004), supported by an unrestricted grant by Aventis Pharmaceuticals, USA, stated: In (some) patients with…late stage [type 2 diabetes], basal insulin can be supplemented with a mealtime bolus of human rapid-acting insulin to produce a more physiologic type of glycemic control'.

Novo Nordisk submitted NovoMix30 attempted to marry this need for a long acting and short acting insulin in a premixed preparation that could be given once, twice or three times a day with meals. This supplemented a patient's basal insulin requirement as well as addressing postprandial needs. The mechanism for this was explained by Luzio *et al* (2004). This combination would be even more effective in the later stages of type 2 diabetes where a basal insulin only might not be adequate.

Novo Nordisk noted that the reduction in HbA_{1c} was greater in patients on NovoMix 30 compared to Lantus, particularly in patients with a higher baseline HbA_{1c} (Raskin *et al* 2005). This was because a basal insulin alone could not control postprandial hyperglycaemia.

Malone *et al* (2005) had published two studies with Lispro Mix 75/25 that came to similar conclusions about meeting HbA_{1c} targets with a premix analogue insulin versus a basal insulin than the INITIATE study. Lispro Mix 75/25 was broadly similar to NovoMix 30 although there was only 25% 'free' lispro insulin in the mix compared to 30% 'free' aspart in NovoMix 30.

Novo Nordisk noted that as diabetes progressed and less endogenous insulin was available to supply type 2 patients on a basal insulin to meet mealtime demands, patients on NovoMix30 would logically be better controlled than patients on Lantus only provided a treat-to-target approach was taken (as in the INITIATE study).

Novo Nordisk reiterated that type 2 diabetes was a progressive disease managed in a stepwise fashion depending on how advanced the disease was. Clear guidelines existed on when insulin should be started for clinicians not to be in any doubt. It was also assumed that insulin therapy would be lifelong when started in a type 2 diabetic.

Novo Nordisk noted that the INITIATE study recruited insulin naïve patients who, according to their HbA_{1c} and their previous medicines, clearly needed insulin. The reason for this was that insulin naïve patients that needed to go onto insulin were the easiest sample to study. Such a patient population would have the least amount of variables to consider in a comparison between two insulin options, making the comparison more objective.

Novo Nordisk submitted that based on the HbA_{1c} variation seen in the patients recruited, quite a few of them had advanced diabetes with very little residual pancreatic function. It could be argued that they should have been put on insulin many years before and represented the later stages of type 2 diabetes in this study. The cohort of patients in the INITIATE study was representative of all patients that would need 'stage 3 treatment' ie type 2 diabetics that needed insulin.

Novo Nordisk submitted that type 2 diabetics on insulin should also be on an insulin sensitizer. The only insulin sensitizer currently approved for use with insulin in the UK was metformin. Only patients that could not tolerate metformin due to gastrointestinal upset or in whom it was contraindicated, would not be using this.

Novo Nordisk noted that the advertisement at issue compared the two regimes most often used to start insulin in type 2 diabetics – once daily Lantus and twice daily NovoMix 30. It specifically compared the proportion of patients that reached the recommended HbA_{1c} target of 7% on the two treatment options.

Novo Nordisk submitted that as a comparative advertisement, it was designed to make a health professional think about the choice between two insulin treatment options available to a type 2 diabetic, all other things being equal. The advertisement could not mislead a doctor into prescribing insulin for inappropriate indications. The INITIATE study population represented 'stage 3' patients ie those that had failed on oral medicine. This included the late stage of diabetes as some of the patients had quite high HbA_{1c} levels and responded to both insulin regimes.

Novo Nordisk did not consider that the advertisement was misleading. Clear guidelines existed recommending when insulin should be started in type 2 diabetics. When they were started on insulin, it was for life. The 'stage' of type 2 diabetes that the advertisement implied was thus clearly defined by guidelines. It was all patients with type 2 diabetes that needed insulin. As the advertisement compared two insulin regimes in this group, the focus should be in the choice of insulin to start with, not when to start it.

Novo Nordisk submitted that metformin was used in both arms of the trial and was thus not relevant in the comparison of the two insulins. Again, clear guidelines existed for when a patient should not be taking metformin with insulin and no health professional should be confused in that respect by this comparison between two insulin options. Continuing metformin was such standard practice in the UK that only the omission of this agent would have been worthy of comment and further explanation.

Novo Nordisk submitted that the advertisement was not in breach of Clause 7.10 of the Code, as the claim in comparing the two insulin choices was not

exaggerated or all-embracing. No special merit was implied. As this was a comparative advertisement mentioning type 2 diabetes and insulin, the group of patients in question should be clear to the health professional.

COMMENTS FROM SANOFI-AVENTIS

Sanofi-Aventis referred to a recent newsletter from the Medicines and Healthcare products Regulatory Agency (MHRA) (No.148 March/April 2005), which it considered succinctly summed up its position:

'Where secondary endpoint data are being used to promote a product, primary endpoint data and the limitations [emphasis added] of the data must be included too.'

'Presenting selected data may exaggerate the benefits of the product and be considered to be in breach of the legislation. We have taken action to correct misleading advertising on the basis of weak comparisons and to ensure that advertising contains information that is sufficiently complete to allow the data to be set in context so that the significance of the findings can be evaluated.'

'Care should be taken to present all relevant data to ensure that fair and balanced comparisons can be made, so that any conclusions derived from the advertisement lead to rational prescribing of a product.'

Sanofi-Aventis noted that the INITIATE study had been subject to much discussion in the UK and the US. Indeed, in the same edition of the journal, an editorial (Davidson 2005) compared this to another study (Janka *et al* 2005). This month, two letters to the editor (Mikhail *et al* 2005 and Janka 2005) had commented on the comparison of these studies.

For each of Clause 7.3 and 7.10, Sanofi-Aventis requested that the Appeal Board considered two points: the limitations of the INITIATE study with respect to methodology (target population, concomitant medication and dose schedule) and its impact on results and the emerging clinical and scientific opinion in the context of other available data.

Sanofi-Aventis noted that the target population of the INITIATE study was insulin naïve patients with type 2 diabetes. As type 2 diabetes was a progressive chronic illness, this group of patients had very different insulin requirements in those type 2 diabetics who had been on insulin for many years.

Sanofi-Aventis alleged that concomitant medication was not addressed in the advertisement at issue and it remained unclear that this subgroup were not taking TZDs. The most important limitations and sources of bias in the study were: the design and implementation of dose titrations and schedules and the population to which the improvement occurred. The importance of fasting blood glucose (FBG) targets related to optimising basal insulin dose – ie the highest dose without hypoglycaemia. The definition of 'without hypoglycaemia' varied according to individual protocols, but was generally accepted as documented significant hypoglycaemia (blood glucose <72mg/dL). The FBG titrations for both insulins were 80-110mg/dL which was sub-optimal for Lantus. The optimal FBG target for Lantus was 100mg/dL. However, as NovoMix 30 had basal and prandial insulin components and had a peaked pharmacodynamic profile, using a lower FBG target ≤ 100mg/dL, which was optimised for Lantus would likely result in a greater rate of significant hypoglycaemia for NovoMix 30.

Sanofi-Aventis alleged that firstly, the claim referred to a secondary endpoint as well as that of a subgroup without referencing this fact. This was in contravention to the recent MHRA newsletter. Furthermore, the font size of '60%' (~ 20% of the height of the page) was highly emphasised for a secondary endpoint. Secondly, while the primary endpoint (improvement in HbA_{1c} from baseline to the end of the study) favoured NovoMix 30, it could be understood in terms of the ~ 50% greater dose than Lantus (78.5 and 51.3 units) which remained essentially unchanged when expressed as units by weight (0.82 vs 0.55 units/kg). This was concisely explained by Mikhail *et al*. This was important data for a clinician to consider when deciding treatment as dose was closely linked to weight change and hypoglycaemia.

Lastly, the authors found no significant decrease in HbA_{1c} between the two insulins in patients with baseline HbA_{1c} < 8.5% while those patients with HbA_{1c} ≥ 8.5% accounted for the difference between the two groups (HbA_{1c} decrease of –3.1 vs –2.6%) (Raskin *et al* and Davidson). This was also important data to consider for prescribing decisions.

Emerging clinical and scientific opinion

Sanofi-Aventis noted that Janka *et al* also compared Lantus to NovoMix 30. However, the similarities between Janka *et al* and the INITIATE study ended there. In Janka *et al*, the primary endpoint of HbA_{1c} improvement from baseline to the end of the study significantly favoured the Lantus group. Differences in this study design to the INITIATE study included: a human biphasic insulin; no oral agents were used in that arm and FBG targets were ≤100mg/dL.

Sanofi-Aventis submitted that it was also important to consider the clinical side effects related to insulin dose – weight and hypoglycaemic events in evaluating the risk-benefit profile (Davidson, Mikhail *et al*, Janka) which in turn were influenced by the study design, especially titration targets.

Sanofi-Aventis alleged that finally, the use of Lantus in Janka *et al* did not preclude the use of additional prandial (meal-time) insulin. In normal practice, if patients did not reach target HbA_{1c} with basal insulin alone, prandial insulin would be added. This could help improve compliance and avoided unnecessary use of prandial insulins in those who did not require it.

In summary, Sanofi-Aventis alleged that the simple claim 'In type 2 diabetes, 60% more people reached HbA_{1c} ≤7% with twice daily NovoMix30 compared to insulin glargine', did not allow health professionals to judge the clinical significance of it by understanding the data within the context of the study's limitations,

the population the claim was referring to and also emerging clinical and scientific opinion. Thus Sanofi-Aventis strongly considered that the Panel's rulings of breaches of Clauses 7.3 and 7.10 should be upheld.

APPEAL BOARD RULING

The Appeal Board noted that the claim '60% more people reached HbA_{1c} target of <7% with twice daily NovoMix 30 compared with insulin glargine' related to a very specific group of type 2 diabetics, ie insulin naïve patients who had insulin added to metformin therapy because they were inadequately controlled on optimal doses of metformin alone. Conversely, by giving so few details about the patient population at issue, the advertisement implied that the claim applied to all type 2 diabetics which was not so. The Appeal Board considered that the claim was misleading and exaggerated in that regard and upheld the Panel's rulings of breaches of Clauses 7.3 and 7.10 of the Code. The appeal was thus unsuccessful.

Complaint received **23 March 2005**

Case completed **14 July 2005**

CASE AUTH/1701/4/05

ASTRAZENECA/DIRECTOR v GLAXOSMITHKLINE

Seretide journal advertisement

AstraZeneca complained that a journal advertisement for Seretide (salmeterol and fluticasone), was, *inter alia*, in breach of an undertaking previously given by GlaxoSmithKline. That part of the complaint was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings.

AstraZeneca further noted that the advertisement was headed 'Different types of asthma patient. One feeling of CONTROL'. As the advertisement focussed on the treatment of asthma with Seretide then 'CONTROL' in the headline implied that all patients who took Seretide would be able to achieve the same level of asthma control.

The main text of the advertisement stated 'GOAL, a new landmark study, has shown that TOTAL CONTROL (assessed for 7 out of 8 weeks) is achievable with Seretide in up to 44% of patients previously uncontrolled on inhaled corticosteroids alone. It's a freedom they never thought possible'. AstraZeneca considered that the use of capitals, its position next to the Seretide logo and the prominence of the text would mislead the reader into assuming that the control mentioned in the headline and in the body text were the same thing, therefore implying that Seretide provided total control of asthma. The advertisement did not define the composite endpoint that constituted 'total control', the reader was allowed to form an open interpretation on what total control actually meant hence further compounding the impression that Seretide could provide the feeling of 'total control'.

AstraZeneca noted that in Case AUTH/1635/9/04 the Panel had ruled that Seretide did not provide total control of asthma; the results from the GOAL study did not support that Seretide could provide total control for all asthma patients. AstraZeneca alleged that the claim within the main text of the advertisement was misleading.

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

The Panel noted that in Case AUTH/1635/9/04, GlaxoSmithKline had been ruled in breach of the Code for implying that Seretide could provide total control of asthma which was not so. The 'total control' referred to was that as defined in the GOAL study not 'total control' *per se*. Readers would not appreciate the subtle difference.

Turning to the advertisement at issue, the Panel noted that the copy was limited to a headline, a small body of text and the product logo and strapline; within the context of this Seretide advertisement, each element would be seen as a claim for the product. Readers were likely to assume that the headline 'Different types of asthma patient. One feeling of CONTROL' implied that all asthmatics treated with Seretide achieved a uniform standard of control. The words 'CONTROL' and 'TOTAL CONTROL' appeared in upper case in the headline and body of text respectively. The Panel considered that readers would link the two statements and assume that Seretide provided total control of asthma. This impression was strengthened by the fact that total control was not defined, the body of text referred to total control being achievable with Seretide in patients previously *uncontrolled* (emphasis added) on inhaled corticosteroids alone and the strapline 'Aim for a life without symptoms'. The Panel considered that the impression that all asthmatics achieved total control with Seretide was misleading, exaggerated and not capable of substantiation. Breaches of the Code were ruled. The Panel further considered that GlaxoSmithKline had breached its undertaking given in Case AUTH/1635/9/04 and a further breach was ruled.

AstraZeneca stated that the emphasis on asthma control was not supported by the GOAL study. The advertisement indicated that up to 44% of patients actually achieved 'total control' rather than 100% of patients that would be needed to substantiate total control of asthma.

Patients entered into the GOAL study were equally divided into three groups depending upon their severity of asthma; groups 2 and 3 were those for whom Seretide would normally be indicated. The 44% in the main text of the advertisement related only to group 2 patients who achieved the measure of 'total control' at some point during the 52-week study. Only 29% of patients in group 3 managed to achieve the endpoint of 'total control'. AstraZeneca alleged that 44% represented a selective use of the best data from the study and did not fully reflect the patient population from the GOAL study that would be considered appropriate for the use of Seretide.

The Panel noted that the 44% of patients who achieved 'total control' of asthma, as defined in the GOAL study, were in group 2 ie patients uncontrolled on ≤ 500mcg beclomethasone daily or equivalent. This was not explained in the advertisement. The Panel considered that when referring to results, the phrase 'up to' rarely negated the impression that a particular result would always be achieved. In that regard the Panel considered that the advertisement thus implied that 44% of all asthmatics, previously uncontrolled on inhaled corticosteroids alone, would achieve total control as defined in the GOAL study which was not so. The Panel noted that patients prescribed Seretide would encompass groups 2 and 3 of the GOAL study. If the results of groups 2 and 3 were combined then less than 40% of all of the patients perceived by doctors as suitable candidates for Seretide would achieve 'total control' as defined in the GOAL study. The Panel considered that the claim 'up to 44% of patients' was misleading, exaggerated and could not be substantiated. Breaches of the Code were ruled.

The strapline 'Aim for a life without symptoms' appeared beneath the Seretide product logo. AstraZeneca agreed that the aim for all asthmatics should be '…a life without symptoms' but considered that placing this strapline next to the Seretide logo in the context of the advertisement implied that a life without symptoms was possible for patients on Seretide. 'Total control' was measured for a 7 out of 8 week period, not the entire 52-week duration of the GOAL study. As asthma was a variable disease it was misleading to imply that any results seen over one 8 week period could be sustained throughout the course of the disease, as the phrase 'a life without …' did. In addition, only the minority of patients across all strata achieved the level of 'Total control'.

The Panel considered that with regard to asthma, 'a life without symptoms' was in effect, total control. Although the claim was prefaced with 'Aim for', in the context of the advertisement at issue the strapline strengthened the misleading impression that total, unequivocal control of asthma was achievable with Seretide. This was not so. Breaches of the Code were ruled.

AstraZeneca UK Limited complained about a journal advertisement (ref SFL/DPS/04/16948/1) for Seretide (salmeterol and fluticasone) issued by GlaxoSmithKline UK Ltd. That part of the complaint which involved an alleged breach of undertaking was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with guidance previously given by the Code of Practice Appeal Board.

1 Claim 'One feeling of CONTROL' linked to 'TOTAL CONTROL'

COMPLAINT

AstraZeneca noted that the advertisement was headed 'Different types of asthma patient. One feeling of CONTROL'. As the advertisement focussed on the treatment of asthma with Seretide then 'CONTROL' in the headline implied a uniform level of asthma control. The headline implied that all patients who took Seretide would be able to achieve the same level of asthma control.

The main text of the advertisement stated 'GOAL, a new landmark study, has shown that TOTAL CONTROL (assessed for 7 out of 8 weeks) is achievable with Seretide in up to 44% of patients previously uncontrolled on inhaled corticosteroids alone. It's a freedom they never thought possible'. AstraZeneca considered that the use of capitals, its position next to the Seretide logo and the prominence of the text would mislead the reader into assuming that the control mentioned in the headline and in the body text were the same thing, therefore implying that Seretide provided total control of asthma. Also, as the advertisement did not define the composite endpoint that constituted 'total control', the reader was allowed to form an open interpretation on what total control actually meant and hence further compounded the impression that Seretide could provide the feeling of 'total control'.

In Case AUTH/1635/9/04 the Panel had ruled that Seretide did not provide total control of asthma; the results from the GOAL study did not support that Seretide could provide total control for all asthma patients.

AstraZeneca alleged that the claim within the main text of the advertisement was misleading in breach of Clauses 7.2, 7.4, 7.10 and 22 of the Code.

RESPONSE

GlaxoSmithKline noted that the advertisement was headed 'Different types of asthma patient. One feeling of CONTROL'. The accompanying visual of different people engaged in different activities in a park illustrated that asthmatics should be able to participate in everyday activities, just like other people, not compromised by symptoms of their condition.

It was clearly an aspirational statement and visual, but was in line with the British Thoracic Society/ Scottish Intercollegiate Guidelines Network (BTS/SIGN) British Guideline on the Management of Asthma, which stated that 'The aims of pharmacological management of asthma are the control of symptoms, including nocturnal symptoms and exercise-induced asthma, prevention of exacerbations and the achievement of the best possible pulmonary function with minimum side-effects'.

The term '**control** of symptoms' took primary position as the aim of treatment in the BTS/SIGN statement and its use in the advertisement was entirely consistent with these guidelines.

GlaxoSmithKline noted that the headline made no claim for Seretide; the company did not accept that the aspirational headline implied that all patients who took Seretide would be able to achieve the same level of control and it would not expect prescribers to interpret the statement in that way. 'Control' was often used as an aspiration or therapeutic aim in pharmaceutical advertising in disease areas that required ongoing therapy. This further supported the fact that prescribers would not interpret the headline in the way that AstraZeneca alleged. Moreover, the ruling in Case AUTH/1635/9/04 was with regard to the statement of 'total control' and the definition thereof, and not the more general notion of control in asthma. GlaxoSmithKline denied any breach of its undertaking.

GlaxoSmithKline drew attention to the main text in the advertisement that 'GOAL, a new landmark study, has shown that TOTAL CONTROL (assessed for 7 out of 8 weeks) is achievable with Seretide in up to 44% of patients previously uncontrolled on inhaled corticosteroids alone. It's a freedom they never thought possible'.

The company did not consider that, in the advertisement at issue, there had been a breach of undertaking on the grounds that total control was firstly clearly linked as an outcome measure of the GOAL study, and secondly there was a clear statement regarding the percentage of patients receiving Seretide who achieved total control (ie up to 44%). GlaxoSmithKline understood, as a result of Case AUTH/1635/9/04, that the two issues of linking total control to the GOAL study and definition of the percentage of patients who achieved total control with Seretide were of particular concern and would be a requirement in all future promotional materials. GlaxoSmithKline considered that it had fully complied, in good faith, with this and the reader could not be misled into believing that Seretide provided total control of **all** asthma patients, as AstraZeneca alleged.

GlaxoSmithKline denied any breach of undertaking or that the claim within the main text was misleading or in breach of Clauses 7.2, 7.4, 7.10 and 22 of the Code.

PANEL RULING

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

The Panel noted that in Case AUTH/1635/9/04, GlaxoSmithKline had been ruled in breach of the Code for promotional material which implied that Seretide could provide total control of asthma, which was not so. The 'total control' referred to was that as defined in the GOAL study not 'total control' *per se*. Readers would not appreciate the subtle difference.

Turning to the advertisement at issue, the Panel noted that the copy was limited to a headline, a small body of text and the product logo and strapline. The Panel considered that, contrary to GlaxoSmithKline's submission, within the context of this Seretide advertisement, each element of copy would be seen as a claim for the product. It was unlikely that readers would view the headline 'Different types of asthma patient. One feeling of CONTROL' as an aspirational statement; they were more likely to assume it implied that all asthmatics treated with Seretide achieved a uniform standard of control. The words 'CONTROL' and 'TOTAL CONTROL' appeared in upper case in the headline and body of text respectively. The Panel considered that the reader's eye would link the two statements; readers would assume that Seretide provided total control of asthma. This impression was strengthened by the fact that there was no definition for total control, the body of text referred to total control being achievable with Seretide in patients previously **uncontrolled** (emphasis added) on inhaled corticosteroids alone and the strapline 'Aim for a life without symptoms'. The Panel considered that the impression that all asthmatics achieved total control with Seretide was misleading, exaggerated and not capable of substantiation. Breaches of Clauses 7.2, 7.4 and 7.10 were ruled. The Panel further considered that GlaxoSmithKline had breached its undertaking given in Case AUTH/1635/9/04. A breach of Clause 22 was ruled.

2 Selective use of GOAL results

COMPLAINT

AstraZeneca stated that the emphasis on asthma control was not supported by the GOAL study results. The advertisement indicated that up to 44% of patients actually achieved 'total control' rather than 100% of patients that would be needed to substantiate total control of asthma.

Patients entered into the GOAL study were equally divided between the following three strata: stratum 1, no inhaled steroid ('steroid-naïve'); stratum 2, ≤ 500mcg beclomethasone diproprionate daily or equivalent and stratum 3, >500 to ≤ 1000mcg beclomethasone diproprionate daily or equivalent. This reflected the relative severity of asthma for the patients entering the study.

Seretide was indicated for the treatment of asthmatics not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting beta-2-agonists. Thus the patients appropriate for starting Seretide would be those in strata 2 and 3 combined as defined by the pre-study dose of inhaled steroid above.

In addition, according to the BTS guidelines, patients with moderate to severe asthma (>400 to <800mcg/day beclomethasone equivalent) were the target population for the addition of a long-acting beta-2-agonist to their inhaled steroid.

The 44% figure quoted in the main text of the advertisement was taken specifically only from the stratum 2 patients who achieved the measure of 'total control' at some point during the 52-week study and not from stratum 3. According to the published study

only 29% of patients in stratum 3 managed to achieve the endpoint of 'total control'.

AstraZeneca stated that 44% represented a selective use of the best data from the study that did not fully reflect the patient population studied in the GOAL study that would be considered appropriate for the use of Seretide according to its summary of product characteristics (SPC) and UK asthma guidelines.

AstraZeneca alleged that the selective use of this data from the study was in breach Clauses 7.2, 7.4 and 7.10 of the Code.

RESPONSE

GlaxoSmithKline stated that 5068 patients were screened for inclusion in the GOAL study, and 3416 patients, who were defined as uncontrolled in the run-in period, were randomised into 3 strata as noted by AstraZeneca (stratum 1, n=1098; stratum 2, n=1163 and stratum 3, n=1155).

The GOAL study was designed and powered as three separate, large (n>1,000) studies. Results from each stratum were therefore not subsets of data; they were individually-powered, robust studies in their own right. This was clearly stated in the methods section of the GOAL paper (Bateman *et al* 2004) and reinforced in the accompanying editorial (Barnes 2004).

As noted by AstraZeneca, Seretide was indicated for the treatment of asthma patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting beta-2- agonists. GlaxoSmithKline had been careful, therefore, to only present data relating to patients within the licensed indication for Seretide, ie stratum 2 and 3 patients, as per the ruling in Case AUTH/1635/9/04.

Results from the GOAL study for patients achieving 'total control' with Seretide were as follows: 50% of stratum 1, 44% of stratum 2 and 29% of stratum 3. As a consequence, GlaxoSmithKline considered that the claim in the main text '…. is achievable with Seretide in **up to** 44% of patients …..' was appropriate, accurate and complied with the Code.

GlaxoSmithKline refuted the allegation that the advertisement 'cherry-picked' the results and was designed to mislead the reader – indeed, AstraZeneca alleged that only stratum 2 results were presented, but this was not so, as the statement in the main text clearly stated up to 44%, not a categorical 44%.

GlaxoSmithKline denied breaching Clauses 7.2, 7.4 and 7.10 of the Code.

PANEL RULING

The Panel noted that the 44% of patients who achieved 'total control' of asthma, as defined in the GOAL study, were in stratum 2, ie patients uncontrolled on ≤ 500mcg beclomethasone daily or equivalent. This was not explained in the advertisement. The Panel considered that when referring to results, the phrase 'up to' rarely negated the impression that a particular result would always be achieved. In that regard the Panel considered that the advertisement thus implied that 44% of all asthmatics, previously uncontrolled on inhaled corticosteroids alone, would achieve total control as defined in the GOAL study, which was not so. The Panel noted that patients prescribed Seretide would encompass both strata 2 and 3 of the GOAL study. If the results of both strata 2 and 3 were combined then less than 40% of all of the patients perceived by doctors as suitable candidates for Seretide would achieve 'total control' as defined in the GOAL study.

The Panel considered that the claim 'up to 44% of patients' was misleading, exaggerated and could not be substantiated. Breaches of Clauses 7.2, 7.4 and 7.10 were ruled.

3 Strapline 'Aim for a life without symptoms'

This appeared beneath the Seretide product logo.

COMPLAINT

AstraZeneca agreed that the aim for all asthmatics should be '…a life without symptoms' but considered that the placement of this strapline next to the Seretide logo in the context of the advertisement implied that a life without symptoms was possible for patients on Seretide.

'Total control' was measured for a 7 out of 8 week period, not the entire 52-week duration of the GOAL study. As asthma was a variable disease it was misleading to imply that any results seen over one 8 week period could be sustained throughout the course of the disease, as the phrase 'a life without …' did. In addition, only the minority of patients across all strata achieved the level of 'Total control'.

AstraZeneca alleged that the strapline was in breach of Clauses 7.2, 7.4 and 7.10 of the Code.

RESPONSE

GlaxoSmithKline submitted that the strapline was an aspirational statement. Aiming for a life without symptoms of asthma should be something to which both patients and health practitioners aspired, and was in line with aims of the pharmacological management of asthma as set out in the BTS/SIGN British Guideline on the Management of Asthma. GlaxoSmithKline considered that Seretide could play an important part in working towards that aim and was entirely within the letter and spirit of the Code.

There was an important distinction between the Seretide logo cluster appearing with the strapline 'Aim for a life without symptoms' and the detail of the complaint which referred to the claim 'a life without [symptoms]'. The selective quoting of the strapline by AstraZeneca did not however accurately represent the strapline in its entirety. The strapline 'Aim for a life without symptoms' was an aspirational statement of intent, entirely within the letter and the spirit of the Code.

GlaxoSmithKline denied breaches of Clauses 7.2, 7.4 and 7.10 of the Code.

PANEL RULING

The Panel considered that with regard to asthma, 'a life without symptoms' was in effect, total control. Although the claim was prefaced with 'Aim for', in the context of the advertisement at issue the strapline strengthened the misleading impression that total, unequivocal control of asthma was achievable with Seretide. This was not so. Breaches of Clauses 7.2, 7.4 and 7.10 were ruled.

Complaint received **19 April 2005**

Case completed **13 July 2005**

CASE AUTH/1702/4/05

CONSULTANT NEUROLOGIST v ALLERGAN

Advisory board meeting

A consultant neurologist questioned whether an offer from Allergan of a £500 honorarium, in addition to the reimbursement of travel expenses, to attend a 'Botox Dystonia Forum' was in breach of the Code. The invitation to the meeting stated that, *inter alia*, presentations, workshops and discussions would consider new data on the differentiation between toxins, antigenicity, neurotoxins in pain; there would also be an update on patient research presented by the Dystonia Society. The meeting would be held at a named hotel and last from 12.30pm on a Friday until 1pm the following day.

The Panel noted that the complainant had not attended the meeting in question, the complaint had been made on the basis of the invitation sent by Allergan.

The Panel was concerned about the impression given by the invitation. There was no mention that, as submitted by Allergan, the meeting was an advisory board or of the contribution and work expected from the invitees. It appeared that health professionals were simply being paid to attend a meeting at an exclusive venue. The Panel considered that in this regard the arrangements for the meeting were unacceptable. The offer to pay an honorarium in conjunction with the details as stated in the invitation was inappropriate and a breach of the Code was ruled.

The Panel noted that whilst the meeting venue was ultimately changed some invitations were issued on the basis that it would be held at the exclusive and luxurious hotel. The Code referred to the offer of hospitality at meetings. Invitations to meetings were covered even if the meeting ultimately took place at a different venue. In this regard the Panel considered that the offer of hospitality at the hotel was inappropriate and excessive. A breach of the Code was ruled.

The Panel considered that in relation to the invitation, high standards had not been maintained. A breach of the Code was ruled. The Panel considered that, by implying that it was paying doctors to attend a meeting at an exclusive venue, Allergan had brought discredit upon the industry and a breach of Clause 2 was ruled.

A consultant neurologist complained about an invitation to a 'Botox Dystonia Forum' which he had received from Allergan Limited. The invitation stated that the meeting would discuss the profiles of neurotoxins. Presentations, workshops and discussions would consider new data on the differentiation between toxins, antigenicity, neurotoxins in pain and an update on patient research presented by the Dystonia Society. The meeting would be held at a named hotel and last from 12.30pm on Friday 22 April until 1pm the following day. The invitation stated that Allergan would reimburse travel expenses and offer an honorarium of £500.

COMPLAINT

The complainant questioned whether the offer of a £500 honorarium, in addition to the reimbursement of travel expenses was in breach of the Code.

When writing to Allergan, the Authority asked it to respond in relation to Clauses 2, 9.1, 18.1 and 19.1 of the Code.

RESPONSE

Allergan explained that the Botox Dystonia Forum was an advisory board meeting with two key goals: to establish and re-establish relationships with neurologists treating dystonias and to seek advice on Allergan's approach to the dystonia market. The meeting was planned to be held at the hotel named on the invitation but was actually held at a different venue. A full brief on the rationale for the advisory board meeting was provided. This brief was supplied to an external company managing the meeting logistics.

Allergan stated that neurologists with an interest in neurotoxin development were invited to the meeting. The potential delegates were selected based on the criteria in the meeting brief. They were selected regardless of their use of any particular brand or type of neurotoxin. The objective was to obtain an attendance of around 20 neurologists, including the 2 chairmen. Seventeen of the forty neurologists invited, accepted. A list of the 17 attendees was provided. Potential delegates were invited by a non-promotional letter and response system which was managed by the external meeting logistics company. The potential delegates would have received one of two very similar letters depending on the exact date of posting. These letters only varied in the details of the meeting venue, given either as the hotel named on the invitation submitted by the complainant or a 'venue to be confirmed in the south east of England'. Those

who accepted the invitation then received a second letter confirming the new venue.

Allergan stated none of the materials given to the potential delegates prior to the meeting or those used during the meeting were promotional.

Allergan explained that the meeting started, following lunch, at 2pm on Friday 22 April and consisted of an afternoon of presentations as background to the following day's work schedule. This was followed by a dinner in the evening. The next day started with further background material being presented followed by a workshop designed to produce an output in line with any advisory board meeting. The meeting finished at 1pm. The total cost to Allergan for each delegate, including the evening dinner, bed and breakfast was £347.

The delegates received an honorarium of £500 for attendance; the two chairmen each received an honorarium of £1000. The honoraria were provided as recompense for the time spent at the meeting which included active participation in the workshops. In addition, a number of participants were required to prepare material prior to the meeting and present that material at the meeting. With respect to the Chairmen, these honoraria also reflected the additional work required at the meeting and preparation required prior to the meeting. Travelling expenses were based either on actual receipts for business class travel or a mileage allowance if the delegates had used their own cars.

Allergan submitted that, in line with Clause 9.1 of the Code, the organisation for this entirely non-promotional advisory board meeting and the meeting itself were of the highest professional standards. Therefore, the company considered that high standards had been maintained at all times and that this activity was not in breach of Clause 9.1.

Allergan considered that the honorarium of £500 per delegate (and £1000 for each of the chairmen) was entirely reasonable and in line with payments expected for this kind of work. A significant amount of each delegate's professional time was involved and active participation was required from all the attendees. The purpose of the meeting was not to promote a medicine but to impart and gather information. Therefore, the honorarium did not constitute an 'inducement to prescribe' which was prohibited under Clause 18.1 of the Code.

The hospitality provided was in accordance with what a neurologist might expect to pay themselves for an equivalent stay at such a venue. The hospitality was commensurate with that normally extended to attendees at an advisory board meeting and was secondary to the meeting. Allergan did not consider that any hospitality extended was excessive and that Allergan was in complete compliance with Clause 19.1 of the Code.

Allergan considered that its handling of this advisory board meeting was in accordance with good pharmaceutical industry practice and did not discredit or reduce confidence in the pharmaceutical industry. The company denied a breach of Clause 2 of the Code.

PANEL RULING

The Panel noted that the complainant had not attended the meeting in question, the complaint had been made on the basis of the invitation sent by Allergan and the Panel made its ruling on this basis. The Panel did not consider that it had a complaint about the acceptability of the meeting *per se*.

The Panel noted 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 professional and others for advice on subjects relevant to the products they promoted. Nonetheless the arrangements for such meetings had to comply with the Code. As with promotional meetings 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 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. Invitations to participate in an advisory board meeting should state the purpose of the meeting and the expected advisory role and amount of work to be undertaken; it should be clear that the honorarium was a payment for such work and advice.

The invitation in question stated that the planned meeting would be the 'first Botox Dystonia Forum'. An outline of the meeting was given and the attached agenda showed that there would be a mixture of presentations, workshops and discussion periods. The named meeting venue was an exclusive and luxurious hotel.

The Panel was concerned about the impression given by the invitation. There was no mention that the meeting was an advisory board or of the contribution and work expected from the invitees. It appeared that health professionals were simply being paid to attend a meeting at an exclusive venue. The Panel considered that in this regard the arrangements for the meeting were unacceptable. The offer to pay an honorarium in conjunction with the details as stated in the invitation was inappropriate and contrary to the requirements of Clause 18.1; a breach of that Clause was ruled.

The Panel noted that whilst the meeting venue was ultimately changed some invitations were issued on the basis that it would be held at the named exclusive and luxurious hotel. The Code referred to the offer of hospitality at meetings. Invitations to meetings were covered even if the meeting ultimately took place at a different venue. In this regard the Panel considered that the offer of hospitality at the named venue was inappropriate and excessive. A breach of Clause 19.1 of the Code was ruled.

The Panel considered that in relation to the invitation, high standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted that Clause 2 of the Code stated that, *inter alia*, activities associated with promotion must

never be such as to bring discredit upon, or reduce confidence in, the pharmaceutical industry. A ruling of a breach of Clause 2 was a sign of particular censure and reserved for such circumstances. The Panel considered that, by implying that it was paying doctors to attend a meeting at an exclusive venue, Allergan had brought discredit upon the industry. A breach of Clause 2 was ruled.

During its consideration of this case the Panel noted that the meeting had been held at a different hotel to that stated on the invitation which was described as 'a luxury country estate hotel' with a 'world-class' spa.

A letter sent to those who accepted the invitation to the meeting stressed the need to book spa treatments well in advance. Although such treatments were to be at the delegate's expense the Panel was concerned about the impression given by the letter. The Panel also questioned whether £347 per head was more than delegates would have paid for themselves for a 24 hour stay at a hotel. The Panel requested that Allergan be advised of its concerns in this regard.

Complaint received **15 April 2005**

Case completed **26 May 2005**

CASES AUTH/1704/4/05 & AUTH/1711/5/05, AUTH/1706/4/05 & AUTH/1712/5/05 and AUTH/1707/5/05 & AUTH/1713/5/05

PRIMARY CARE TRUST PHARMACIST, GENERAL PRACTITIONER and PRESCRIBING ADVISER v PROCTER & GAMBLE AND SANOFI-AVENTIS

Actonel mailing

A pharmacist at a primary care trust (PCT), a general practitioner and a prescribing adviser complained separately about an Actonel (risedronate sodium) mailing sent jointly by Procter & Gamble and Sanofi-Aventis, which featured information issued by the National Institute for Clinical Excellence (NICE) on the secondary prevention of osteoporotic fragility fractures in postmenopausal women.

The mailing consisted of an A4 document wallet, the front cover of which featured only the statement 'NICE National Institute of [sic] Clinical Excellence'. The inside front cover detailed NICE guidance on the use of bisphosphonates in the treatment of established postmenopausal osteoporosis. The opposite page (the inside back cover) gave details on the use of Actonel (a bisphosphonate) in established postmenopausal osteoporosis. The document wallet also incorporated a pocket flap on the inside front cover which contained an A4 sheet, giving more information on the NICE guidance, and a reply paid card allowing the recipient to request a SIM card saver.

All of the complainants alleged that the presentation of the folder was such as to mislead the reader into assuming that it was an official document from NICE.

The PCT pharmacist further noted that an insert claimed that NICE recommended that 'For women aged between 65 and 74, the Committee felt that, once booked, a long waiting time for a DEXA scan need not prevent initiation of treatment' whereas what NICE actually stated was 'For women between the ages of 65 and 74 years, the Committee considered that alternative causes of fragility fracture should be excluded and therefore treatment is recommended when a T-score of –2.5 SD or below is established by DEXA scanning. The Committee felt that, once booked, a long waiting time for a DEXA scan need not prevent initiation of treatment; if appropriate, treatment can be stopped once the result of the DEXA scan is available'. The complainant considered that the omission of the last sentence changed the context wholly and was thus misleading.

The GP further considered that to link promotional material for Actonel to broad NICE guidance implied that NICE had in some way endorsed Actonel and pointed to an unhealthy link between NICE and the pharmaceutical industry.

The Panel disagreed with the companies' submission that the envelope in which the mailing was sent clearly identified the contents as promotional. The phrase 'If you've got something NICE to say….' was printed along the bottom edge of the envelope and the flap, on the reverse referred to the Alliance for Better Bone Health.

The envelope contained an A4 document wallet, the front cover of which featured only the words 'NICE National Institute of [sic] Clinical Excellence'. The covering letter referred to by the respondents was contained within a flap inside the wallet and so was not immediately visible.

The Panel noted that the cover of the document wallet was printed in denim blue which was close enough to that used on official NICE documents to suggest that it might have been issued by NICE.

The Panel considered that as some recipients would receive the document wallet out of its envelope, having been opened by administrative staff, then if the first they saw of it was the front cover it was possible that they might have thought that it was an official communication from NICE. In the Panel's view promotional documents should be obviously promotional from the outset. The Panel considered that the document wallet was disguised promotion and misleading in that regard; at first glance it appeared to be an official communication from NICE which was not so. Breaches of the Code were ruled.

With regard to the further allegation from the PCT pharmacist, the Panel noted that the A4 sheet which accompanied the mailing gave a brief summary of the NICE guidance. The guidance with regard to women aged 65 to 74 years, as issued by NICE, stated that treatment could be initiated whilst waiting for a DEXA scan and could, if appropriate, be stopped once the result of the scan was known. The A4 sheet in the mailing similarly referred to initiation of therapy whilst awaiting a DEXA scan but did not advise that such treatment could be stopped, if appropriate, once the results were known. The Panel considered, however, that such advice reflected normal medical practice. It was clear that the A4 sheet did not report the NICE guidance in full and nor was the information given therein presented as a quotation from the NICE guidance. The Panel did not consider that the document at issue misled due to the omission of the final part of the NICE guidance. No breach of the Code was ruled.

With regard to the allegation from the GP that the material implied that NICE in some way endorsed Actonel, the Panel noted that although the document wallet detailed both the NICE guidance and Actonel, the two did not appear on the same page. No product specific information appeared on the page referring to the NICE guidance and the NICE guidance was not referred to on the page detailing Actonel. Although the A4 sheet within the document wallet which gave more information on the NICE guidance referred to the use of risedronate, as had the guidance itself, the Panel did not consider that the mailing implied endorsement of Actonel by NICE as alleged. No breach of the Code was ruled.

A primary care trust (PCT) pharmacist, a general practitioner and a prescribing adviser each complained about an Actonel (risedronate sodium) mailing (ref A2689/ACT8170904) sent jointly by Procter & Gamble Pharmaceuticals (UK) Ltd and Sanofi-Aventis. The mailing featured information issued by the National Institute for Clinical Excellence (NICE) on the secondary prevention of osteoporotic fragility fractures in postmenopausal women.

The mailing consisted of an A4 document wallet, the front cover of which featured only the statement 'NICE National Institute of [sic] Clinical Excellence'. The inside front cover detailed NICE guidance on the use of bisphosphonates in the treatment of established postmenopausal osteoporosis. The opposite page (the inside back cover) gave details on the use of Actonel (a bisphosphonate) in established postmenopausal osteoporosis. The back cover featured an Actonel pack shot and the prescribing information. The document wallet also incorporated a pocket flap on the inside front cover which contained an A4 sheet, giving more information on the NICE guidance, and a reply paid card allowing the recipient to request a SIM card saver.

Cases AUTH/1704/4/05 & AUTH/1711/5/05

COMPLAINT

The PCT pharmacist noted that the front cover of the folder had no words other than 'NICE National Institute of Clinical Excellence' and other than the mis-annotation of the name of the official body, the National Institute for Clinical Excellence, it was clear that this had been done to mislead clinicians into believing that it was an official NICE document.

The complainant further noted that an insert claimed that NICE recommended that 'For women aged between 65 and 74, the Committee felt that, once booked, a long waiting time for a DEXA scan need not prevent initiation of treatment' whereas what NICE actually stated was 'For women between the ages of 65 and 74 years, the Committee considered that alternative causes of fragility fracture should be excluded and therefore treatment is recommended when a T-score of –2.5 SD or below is established by DEXA scanning. The Committee felt that, once booked, a long waiting time for a DEXA scan need not prevent initiation of treatment; if appropriate, treatment can be stopped once the result of the DEXA scan is available'. The complainant alleged that the omission of the last sentence changed the context wholly and was misleading in that regard.

Cases AUTH/1706/4/05 & AUTH/1712/5/05

COMPLAINT

The GP stated that on seeing the folder he immediately assumed that this was a communication from NICE and therefore opened it to peruse what he thought was information from an independent body. On opening the folder it was obvious that it was promotional material for Actonel, riding on the back of a NICE recommendation of the use of bisphosphonates. The back of the folder did make it clear that this material was in connection with Actonel.

The complainant was annoyed firstly because he was duped into looking at promotional information because of the disguise of the folder and secondly because he considered that to link promotional material for Actonel to broad NICE guidance implied that NICE had in some way endorsed Actonel and pointed to an unhealthy link between NICE and the pharmaceutical industry.

Cases AUTH/1707/5/05 & AUTH/1713/5/05

COMPLAINT

The prescribing adviser considered that NICE was used to mislead prescribers. The folder was sent to the complainant by a local GP who, together with his colleagues, initially believed that it contained official documents from NICE.

When writing to Procter & Gamble about all three complaints the Authority asked it to respond in relation to the requirements of Clauses 7.2 and 10.1 of the Code.

RESPONSE

Procter & Gamble and Sanofi-Aventis submitted a joint response to each complaint as they had jointly sent the mailing.

All cases

The companies submitted that the material in question was clearly a promotional piece and as such could not be confused with an official communication from NICE.

The envelope in which the document wallet was sent clearly identified the contents as a promotional item by using the strapline 'If you have something NICE to say …'. In addition 'The Alliance for Better Bone Health' was mentioned on the outside of the envelope.

By its look and feel the document wallet itself was obviously a promotional item from a pharmaceutical company; it was colourful with visuals, layout, product branding throughout and with abbreviated prescribing information on the rear. In addition to this the document wallet was accompanied by a covering letter on company headed paper. For these reasons, the companies did not consider that the mailing was likely to be mistaken as a communication from NICE. The companies did not consider that the mailing was misleading or implied that the contents were non-promotional, they denied breaches of Clauses 7.2 and 10.1 of the Code.

Cases AUTH/1704/4/05 & AUTH/1711/5/05

With regard to the further allegation from the PCT pharmacist, the companies disagreed that by omitting one sentence at the end of a paragraph they had modified the information from NICE, changed the context and misled the reader in breach of Clause 7.2 of the Code. In this instance the abbreviated paragraph conveyed the same important information as the full paragraph. The omitted last sentence was common sense for medical practitioners and was standard medical practice. When DEXA results became available, as with any new information, the doctor would assess the current treatment plan and adjust it according to this new information, if required. Thus, the companies were surprised by the suggestion that the context of the paragraph had been changed by removing the phrase 'if appropriate, treatment can be stopped once the results of the DEXA scan is available', since after requesting a DEXA scan a doctor would not continue to treat a patient if the results suggested otherwise.

Cases AUTH/1706/4/05 & AUTH/1712/5/05

With regard to the allegation from the GP that the material implied that NICE in some way endorsed Actonel, the companies submitted that in the mailer they had quoted from or summarized the NICE guidance on the secondary prevention of osteoporotic fragility fractures in postmenopausal women. They had not inserted the brand name Actonel or replaced text used by NICE with brand specific information. The covering letter and the page with information from NICE did not feature additional product specific information. Subsequent pages of the mailing which contained product specific information at no time implied, inferred or even mentioned NICE or a NICE endorsement of Actonel, therefore the companies did not consider that the mailing breached Clause 7.2.

Cases AUTH/1704/4/05 & AUTH/1711/5/05 and AUTH/1706/4/05 & AUTH/1712/5/05

In summary, the companies considered that the mailing was clearly a promotional piece and the information contained therein was accurate, fair, balanced and did not mislead directly or by implication.

PANEL RULING

All cases

The Panel disagreed with the submission that the envelope in which the mailing was sent clearly identified the contents as promotional. The phrase 'If you've got something NICE to say …' was printed along the bottom edge of the envelope and the flap, on the reverse referred to the Alliance for Better Bone Health. The Panel did not consider that recipients of the envelope would automatically know that it contained a promotional mailing from a pharmaceutical company. Nonetheless nor did the Panel consider that the envelope was such as to suggest that it was an official communication from NICE.

The envelope contained an A4 document wallet, the front cover of which featured only the words 'NICE National Institute of [sic] Clinical Excellence'. There was nothing on the front cover to suggest that the wallet had been sent by a pharmaceutical company. It was only when the wallet was opened or turned over that it was obvious that it was promotional material for Actonel. The covering letter referred to by the respondents was contained within a flap inside the wallet and so was not immediately visible.

The Panel noted that the cover of the document wallet was printed in a denim blue colour which, although not exactly the same as the blue used on official NICE documents, was close enough to suggest that it might have been issued by NICE.

The Panel considered that as some recipients would receive the document wallet out of its envelope, having been opened by administrative staff, then if the first they saw of it was the front cover it was possible that they might have thought that it was an official communication from NICE. In the Panel's view promotional documents should be obviously promotional from the outset. The Panel considered that the document wallet was disguised promotion and misleading in that regard; at first glance it appeared to be an official communication from NICE which was not so. Breaches of Clauses 7.2 and 10.1 were ruled.

Cases AUTH/1704/4/05 & AUTH/1711/5/05

The Panel noted that the A4 sheet which accompanied the mailing gave a brief summary of the NICE guidance. The guidance with regard to women aged 65 to 74 years, as issued by NICE, stated that treatment could be initiated whilst waiting for a DEXA scan and could, if appropriate, be stopped once the result of the scan was known. The A4 sheet in the mailing similarly referred to initiation of therapy whilst awaiting a DEXA scan but did not advise that

such treatment could be stopped, if appropriate, once the results were known. The Panel considered, however, that such advice reflected normal medical practice. It was clear that the A4 sheet did not report the NICE guidance in full and nor was the information given therein presented as a quotation from the NICE guidance. The Panel did not consider that the document at issue misled due to the omission of the final part of the NICE guidance. No breach of Clause 7.2 was ruled.

Cases AUTH/1706/4/05 & AUTH/1712/5/05

The Panel noted that although the document wallet detailed both the NICE guidance and Actonel, the two did not appear on the same page. No product specific information appeared on the page referring to the NICE guidance and the NICE guidance was not referred to on the page detailing Actonel. Although the A4 sheet within the document wallet which gave more information on the NICE guidance referred to the use of risedronate as had the guidance itself, the Panel did not consider that the mailing implied endorsement of Actonel by NICE as alleged. No breach of Clause 7.2 was ruled.

Cases AUTH/1704/4/05 & AUTH/1711/5/05
Complaint received 27 April 2005

Cases completed
Case AUTH/1704/4/05 20 June 2005
Case AUTH/1711/5/05 22 June 2005

Cases AUTH/1706/4/05 & AUTH/1712/5/05
Complaint received 6 May 2005

Cases completed
Case AUTH/1706/4/05 20 June 2005
Case AUTH/17/12/5/05 22 June 2005

Cases AUTH/1707/5/05 & AUTH/1713/5/05
Complaint received 9 May 2005

Cases completed
Case AUTH/1707/5/05 20 June 2005
Case AUTH/1713/5/05 22 June 2005

CASE AUTH/1705/5/05

VOLUNTARY ADMISSION v MENARINI

Newspaper article about Migard

Menarini voluntarily advised the Authority that an article about the use of Migard (frovatriptan) to treat menstrual migraine had appeared in the Daily Mail. Migard was developed by Vernalis, which was responsible for its manufacture, but marketed in the US by Endo Pharmaceuticals Inc and in the UK by Menarini. The article was very positive.

The Director of Authority decided that as the matter related to the promotion of a prescription only medicine to the general public it was sufficiently serious for it to be taken up and dealt with as a formal complaint under the Code. This was consistent with advice given by the Code of Practice Appeal Board and published in the August 1997 Code of Practice Review.

The Panel noted that complaints about articles in the press were judged on the information provided by the pharmaceutical company or its agent and not on the content of the article itself. Vernalis in the UK had issued a press release stating that Endo in the US had launched a menstrual migraine campaign. That press release, which was signed off by Menarini, did not mention Migard but did refer readers to the 'attached Endo press release'. The Endo press release gave details of menstrual migraine and how Migard had helped an international tennis star with the condition. The Panel was concerned that Menarini had apparently not insisted on seeing the Endo press release. It was clear that the Vernalis press release was little more than a covering press release for that from Endo. The Endo press release had led to the Daily Mail article in question. Menarini was responsible for the marketing of Migard in the UK and although it had not issued the press release it was an established principle under the Code that companies were responsible for the action of their affiliates. Menarini was therefore responsible for the press release issued in the UK by Vernalis and Endo. The Panel did not consider that the press release was an advertisement *per se* and so ruled no breach of the Code in that regard. The press release did, however, include statements which would encourage members of the public to ask their doctors to prescribe a specific medicine. A breach of the Code was ruled.

COMPLAINT

A. Menarini Pharmaceuticals UK Ltd voluntarily advised the Authority that an article about Migard (frovatriptan) had appeared in the Daily Mail, 3 May 2005. The article entitled 'How a new drug cured tennis champ Serena of her monthly migraine agony' was very positive about the use of Migard to treat menstrual migraine.

The Director of Authority decided that as the matter related to the promotion of a prescription only medicine to the general public it was sufficiently serious for it to be taken up and dealt with as a formal complaint under the Code. This was consistent with advice given by the Code of Practice Appeal Board and published in the August 1997 Code of Practice Review.

The Authority requested that Menarini respond in relation to the provisions of Clauses 20.1 and 20.2 of the Code.

RESPONSE

Menarini submitted that it was not aware until it was too late that the article at issue might appear and at no time did it know what the contents might be.

Menarini explained that frovatriptan was developed by Vernalis which was responsible for its manufacture. Product licences were held by Endo Pharmaceuticals Inc in the US (marketed as Frova) and by Menarini UK SRL in the UK (marketed as Migard) and Europe.

During the last few months Endo had negotiated and developed a campaign to highlight and increase awareness of menstrually related migraine (MRM) with support from Serena Williams who apparently suffered from this condition and had been recruited to promote an awareness campaign called 'RALLY (**R**aise **A**wareness **L**ocal**ly**) for Menstrual Migraine'.

Menarini stated that on 12 April, Vernalis issued a press release (a copy was provided). This was the only document that Menarini saw prior to its release and as it contained no product-related information it was approved and signed off.

Also on 12 April, Endo in the US issued a press release which referred to Serena Williams' involvement and her opinion of frovatriptan (Frova). Menarini stated that the rules referring to the advertisement of prescription medicines to the public in the US were very different from those in the UK and were outwith its control. However Menarini received a copy of the proposed release at 11.33am on April 12 stating that the announcement was to be released 1.30pm UK time, giving the company less than 3 hours to make any comment. This assumed that the email was read immediately on receipt. The press release was issued together with background material and a link to a website. Endo also arranged for satellite feeds direct from the US to all the major news channels. When Menarini received this information it replied that it was 'very late in the day' to be able to approve any of this to be in line with the Code.

On Monday, 2 May (bank holiday) an email was sent to Menarini at 6.06pm from the Head of Corporate Communications at Vernalis, alerting the company that an article might appear in the Daily Mail the following morning subject to final sign off. That email was not opened until early the following morning by which time the article had been published. The first Menarini knew about it was when it saw it in print.

The events described above led to a strong protest to Vernalis about the lack of time allowed for approval. The company was told that it had placed Menarini in a very precarious position with regard to the Code.

On 3 May Menarini telephoned the Authority to report the article and ask for advice. On the same day the Migard marketing team issued a briefing letter to all the sales force informing the representatives of their responsibilities and reminding them that they must not under any circumstance discuss the article or promote Migard outside its licence.

Menarini submitted that as far as it was aware, until this issue arose, Vernalis knew and understood the requirements of the Code. In the UK the marketing of Migard was entirely in the control of Menarini and did not impinge into Vernalis' area of responsibility.

Overall the train of events was unexpected and Menarini was given no chance of any input into the release to the British media. Menarini stated that it had subsequently had discussions with Vernalis and drawn up a process to ensure, as far as it could, that this could not happen again.

Menarini considered that it could not deny that as it appeared the article was in breach of Clauses 20.1 and 20.2 of the Code but it hoped that the unforeseen circumstances would be taken into account.

PANEL RULING

The Panel noted that complaints about articles in the press were judged on the information provided by the pharmaceutical company or its agent to the journalist and not on the content of the article itself. Clause 20.1 prohibited the advertising of prescription only medicines to the general public. Clause 20.2 permitted information to be supplied directly or indirectly to the general public but such information had to be factual and provided in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their doctor to prescribe a specific medicine.

The Panel noted that Vernalis in the UK issued a press release on 12 April stating that its licensing partner in the US, Endo Pharmaceuticals Inc, had launched 'RALLY for menstrual migraine' with Serena Williams. That press release, which was seen and signed off by Menarini, did not refer to Migard but did instruct readers to 'See attached Endo press release'. The Endo press release gave details of menstrual migraine and how Serena Williams suffered from the condition. Serena Williams was quoted as stating 'I really struggled with menstrual migraine, but using Frova [Migard] has really helped me'. The Endo press release also referred to the 'RALLY for menstrual migraine', campaign, gave a brief overview of the efficacy and safety of Frova and some information about Endo. The Panel was concerned that Menarini had apparently not insisted on seeing the Endo press release, which was referred to in the Vernalis press release, before it signed off the Vernalis press release. It was clear that the Vernalis press release was little more than a covering press release for the news release from Endo.

The Panel noted that the Endo press release had resulted in the very positive article about Migard which had appeared in the Daily Mail. Menarini was responsible for the marketing of Migard in the UK and although it had not issued the press release it was an established principle under the Code that companies were responsible for the actions of their affiliates. Menarini UK was therefore responsible for the press release issued in the UK by Vernalis and Endo.

The Panel did not consider that the press release constituted an advertisement for a prescription only medicine to the general public. No breach of Clause

20.1 was ruled. The press release, however, did include statements which would encourage members of the public to ask their doctors to prescribe Migard. A breach of Clause 20.2 was ruled.

Complaint received **6 May 2005**

Case completed **13 June 2005**

CASES AUTH/1709/5/05 and AUTH/1710/5/05 *NO BREACH OF THE CODE*

PFIZER v LILLY and BOEHRINGER INGELHEIM

Promotion of Cymbalta

Pfizer complained about the promotion of Cymbalta (duloxetine) by Lilly and Boehringer Ingelheim. Cymbalta was licensed for the treatment of major depressive episodes. The two claims at issue 'A journey from darkness – helping relieve the suffering, mind and body – into the light' and 'because depression hurts', which was a strapline beneath the Cymbalta product logo, had appeared in two journal advertisements and a mailing.

'Pfizer submitted that the word 'body' in the context of '… the suffering, mind and body' of the first claim, implied physical suffering. With regard to the strapline 'because depression hurts', Pfizer stated that the normal use and understanding of 'hurt' related to physical pain.

Pfizer alleged that the claims were misleading and not consistent with the marketing authorization as they emphasised the importance of treating physical suffering and pain that could be associated with depression, and implied that Cymbalta treated these physical symptoms rather than the depression itself.

Pfizer further noted that as duloxetine was expected to be additionally licenced to treat diabetic peripheral neuropathic pain, the claims might also be considered to be in breach of the Code.

The Panel noted that Cymbalta was licensed to treat major depressive episodes; the summary of product characteristics (SPC) referred to improvements in the emotional and somatic symptoms of depression. The Panel noted the companies' submission that there was clear recognition that many depressed patients experienced physical as well as emotional symptoms.

The Panel considered that although the claim 'A journey from darkness – helping relieve the suffering, mind and body – into the light' referred to physical suffering, this was in the context of mental suffering. The claim '… because depression hurts' would be read as a reference to both emotional and physical hurt. The Panel did not accept Pfizer's view that 'hurt' was normally used and understood as being related to physical pain. The dictionary definition included both physical and mental pain.

The Panel did not consider that the claims emphasised treatment of physical suffering that could be associated with depression rather than the depression itself. The Panel did not consider that the claims were misleading in this regard nor inconsistent with the marketing authorization, and each was ruled not to be in breach of the Code.

The Panel noted Pfizer's comment that Cymbalta was expected to gain an additional indication as a treatment for diabetic peripheral neuropathic pain. The claims at issue did not imply that Cymbalta was for treating pain *per se*. Thus the Panel ruled no breach of the Code.

Pfizer Limited complained about the promotion of Cymbalta (duloxetine) by Eli Lilly and Company Limited and Boehringer Ingelheim Limited. The two claims at issue had appeared in two journal advertisements (refs DDP186 and DDP187) and a mailing (ref DDP153a).

The first claim at issue was 'A journey from darkness – helping relieve the suffering, mind and body – into the light'. The second claim 'because depression hurts' appeared as a strapline beneath the Cymbalta product logo.

COMPLAINT

With regard to the first claim Pfizer submitted that the use of the word 'body' in the context of '… the suffering, mind and body' implied physical bodily suffering. With regard to the strapline 'because depression hurts', Pfizer stated that the normal use and understanding of 'hurt' related to physical pain.

Pfizer alleged that the claims emphasised the importance of treating physical suffering and physical pain that could be associated with depression rather than the depression itself. The advertisements implied that Cymbalta was a treatment for physical symptoms and pain that patients with depression might have rather than the depression itself. The claims were alleged to be misleading and not consistent with the marketing authorization, which clearly stated that Cymbalta was licensed for the treatment of major depressive episodes. A breach of Clause 7.2 was alleged.

Pfizer further noted that duloxetine was expected to gain an additional licence as a treatment for diabetic peripheral neuropathic pain. In light of this, the claims might also be considered to be in breach of Clause 3.2.

RESPONSE

Lilly and Boehringer Ingelheim submitted a joint response.

The companies noted that Cymbalta was licensed for the treatment of major depressive disorder. It was

well recognised that depression itself affected both mind and body. The emotional symptoms of depression included, *inter alia*, low mood, anhedonia and guilt, whereas the bodily (somatic) symptoms included, among others, lack of energy, disturbed sleep, change in appetite and aches and pains. That depression involved both somatic and emotional components was reflected in the DSM IV international classification for mental disorders which stated 'some individuals (with depression) emphasise somatic complaints e.g. bodily aches and pains, rather than reporting feelings of sadness' and in the Hamilton Depression Rating Scale (HAM-D) which had a specific item on somatic symptoms.

Furthermore, there was clear recognition in the published literature of a range of such symptoms in the context of depression. For example, Brannan *et al* (2005) referred to 'pain symptoms' such as 'headache, back pain, limb/joint pain, abdominal pain, and chest pain' and Ohayon *et al* (2003) examined 'chronic painful physical conditions' in relation to major depression and specifically cited 'joint/articular, limb, or back pain, headaches or gastrointestinal disorder'. Stahl (2002) referred to 'painful physical symptoms' in depressed patients such as 'headache, abdominal pain, or musculoskeletal pain in the lower back, joints, and neck …'. Fava *et al* (2004) also referred to 'painful physical symptoms' and in that particular paper referred to depressed patients with 'overall pain, headaches, back pain, shoulder pain, interference with daily activity, and time in pain while awake'.

There was thus clear recognition that many depressed patients experienced physical symptoms as well as emotional symptoms.

The beneficial effect of Cymbalta on these somatic symptoms of depression was reflected in Section 5.1 of the Cymbalta summary of product characteristics (SPC) which included the statement that 'Cymbalta demonstrated statistical superiority over placebo as measured by improvement in the 17-item HAMD total score (including both the emotional and somatic symptoms of depression)'.

The claim 'A journey from darkness – helping relieve the suffering, mind and body – into the light' emphasised the emotional and the physical aspects of the symptomatology. It did not emphasise the physical aspects as alleged and was consistent with the marketing authorization.

Similarly, neither did the strapline 'Cymbalta (duloxetine) because depression hurts' emphasise the physical symptoms. The word 'hurt' embraced both physical and mental pain or distress in its common usage. The Oxford English Dictionary defined hurt as: 'cause physical pain or injury to, (of a part of the body) suffer pain, cause mental pain or distress to, feel mental pain or distress'. The strapline also clarified beyond doubt that the context of the advertisement and the indication for Cymbalta was depression.

With regard to the alleged breach of Clause 3.2 on the basis that duloxetine was expected to gain an additional license as a treatment for diabetic neuropathic pain, the companies stated that the basis for this allegation was not expressed further in the complaint. As this indication had nothing to do with depression, was not referred to anywhere in the materials at issue or the associated briefing materials, and no reference was made to diabetes, neuropathic pain or additional indications Lilly and Boehringer Ingelheim submitted that this was irrelevant to the complaint and there was no case to answer.

In summary Lilly and Boehringer Ingelheim submitted that their materials were consistent with current knowledge about the symptoms of depression and the Cymbalta marketing authorization and were not misleading.

PANEL RULING

The Panel noted that Cymbalta was licensed as a treatment of major depressive episodes. Section 5.1 of the SPC, Pharmacodynamic properties, referred to improvements in the emotional and somatic symptoms of depression. The Panel noted the companies' submission that there was clear recognition that many depressed patients experienced physical symptoms as well as emotional symptoms.

The Panel considered that although the claim 'A journey from darkness – helping relieve the suffering, mind and body – into the light' referred to physical suffering, this was in the context of mental suffering. The claim '… because depression hurts' would be read as a reference to both emotional and physical hurt. The Panel did not accept Pfizer's view that 'hurt' was normally used and understood as being related to physical pain. The dictionary definition included both physical and mental pain.

The Panel did not consider that the claims emphasised treatment of physical suffering that could be associated with depression rather than the depression itself. The Panel did not consider that the claims were misleading in this regard nor inconsistent with the marketing authorization. Each was ruled not to be in breach of Clause 7.2 of the Code.

The Panel noted Pfizer's comment that Cymbalta was expected to gain an additional indication as a treatment for diabetic peripheral neuropathic pain. The claims at issue did not imply that Cymbalta was for treating pain *per se*. Thus the Panel ruled no breach of Clause 3.2 of the Code.

Complaint received **18 May 2005**

Case completed **1 July 2005**

CODE OF PRACTICE REVIEW – AUGUST 2005

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

1622/8/04	**Aventis Pharma v Novo Nordisk**	**Levemir mailing**	**Three breaches Clause 7.2 Three breaches Clause 7.4 Breach Clause 7.5 Three breaches Clause 7.10**	**Appeal by respondent**	**Page 3**
1628/9/04	**Aventis Pharma v Novo Nordisk**	**Levemir launch pack**	**Breaches Clauses 9.7 and 20.1**	**Appeal by respondent**	**Page 20**
1637/10/04 and 1638/10/04	**Lilly v GlaxoSmithKline and Bayer**	**Promotion of Levitra**	**Two breaches Clause 3.2 Breach Clause 4.1 Four breaches Clause 7.2 Breach Clause 7.3 Three breaches Clause 7.10**	**Appeal by respondents**	**Page 26**
1648/11/04	**General Practitioner v Pfizer**	**Celebrex 'Dear Healthcare Professional' letter**	**Breaches Clauses 2, 7.2, 7.4, 7.9 and 9.1**	**Appeal by complainant**	**Page 35**
1667/12/04	**Gilead Sciences v Merck Sharp and Dohme**	**Cancidas 'Dear Healthcare Professional' letter**	**Breach Clause 3.2 Four breaches Clause 7.2 Breach Clause 7.4**	**Appeal by complainant**	**Page 46**
1673/1/05	Insulin Dependant Diabetes Trust v Lilly	Humalog advertisement to the public	No breach	Appeal by respondent	Page 56
1674/1/05	Sanofi-Aventis v Pierre Fabre	Navelbine leaflet	No breach	Appeal by complainant	Page 58
1677/2/05	**Gilead Sciences/Director v Pfizer**	**Promotion of Vfend**	**Breach Clause 2 Four breaches Clause 7.2 Five breaches Clause 7.4 Breaches Clauses 7.10, 7.11, 9.1 and 22**	**No appeal**	**Page 61**
1678/2/05	**Member of the Public v Boehringer Ingelheim**	**Activities of representatives**	**Two breaches Clause 9.1 Two breaches Clause 15.4**	**No appeal**	**Page 71**
1679/2/05	**Member of the Public v Novartis**	**Activities of representatives**	**Two breaches Clause 9.1 Two breaches Clause 15.4**	**No appeal**	**Page 74**
1680/2/05	General Practitioner v Novartis	Diovan mailing	No breach	No appeal	Page 77
1681/2/05	**Boehringer Ingelheim v Sankyo Pharma**	**Olmetec journal advertisements**	**Breaches Clauses 7.2, 7.4 and 7.10**	**No appeal**	**Page 79**

1682/2/05 and 1683/2/05	**General Practitioner and Media/Director v AstraZeneca**	**Arrangements for meetings**	**Breach Clause 2 Two breaches Clause 9.1 Two breaches Clause 19.1**	**Appeal by respondent**	**Page 82**
1684/2/05	Media/Director v GlaxoSmithKline	Hospitality at a meeting	No breach	No appeal	Page 89
1685/3/05	**Janssen-Cilag v Lilly**	**Strattera journal advertisements**	**Three breaches Clause 7.2 Breach Clause 7.3**	**Appeal by respondent**	**Page 91**
1686/3/05	**General Practitioner v Janssen-Cilag**	**Promotion of Durogesic to the public**	**Breaches Clauses 2, 9.1 and 20.2**	**No appeal**	**Page 99**
1687/3/05 and 1699/3/05	**Schering Health Care v Teva and Aventis Pharma**	**Copaxone detail aid**	**Breaches Clauses 7.2, 7.3 and 8.1**	**No appeal**	**Page 102**
1688/3/05	**General Practitioner v AstraZeneca**	**Invitation to a meeting for nurses**	**Breaches Clauses 9.1 and 19.1**	**No appeal**	**Page 104**
1690/3/05	**Primary Care Trust Medicines Management and Prescribing Lead v GlaxoSmithKline**	**Provision of a service**	**Breaches Clauses 2, 9.1 and 18.1**	**No appeal**	**Page 106**
1691/3/05	**Shire v Strakan**	**Promotion of Adcal-D_3**	**Breaches Clauses 7.2 and 7.3**	**No appeal**	**Page 109**
1693/3/05 and 1694/3/05	**Lundbeck v Lilly and Boehringer Ingleheim**	**Promotion of Cymbalta**	**Breach Clause 3.2 Six breaches Clause 7.2 Four breaches Clause 7.4 Three breaches Clause 9.1**	**No appeal**	**Page 111**
1695/3/05	**Hospital Employee v AstraZeneca**	**Arrangements for a meeting**	**Breaches Clauses 2, 9.1, 15.2 and 19.1**	**No appeal**	**Page 122**
1696/3/05	Bristol-Myers Squibb v Boehringer Ingelheim	Abstract review	No breach	No appeal	Page 125
1698/3/05	**Sanofi-Aventis v Novo Nordisk**	**NovoMix 30 journal advertismement**	**Breaches Clauses 7.3 and 7.10**	**Appeal by respondent**	**Page 128**
1701/4/05	**AstraZeneca/Director v GlaxoSmithKline**	**Seretide journal advertisement**	**Three breaches Clause 7.2 Three breaches Clause 7.4 Three breaches Clause 7.10 Breach Clause 22**	**No appeal**	**Page 134**
1702/4/05	**Consultant Neurologist v Allergan**	**Advisory board meeting**	**Breaches Clauses 2, 9.1, 18.1 and 19.1**	**No appeal**	**Page 138**
1704/4/05 and 1711/5/05, 1706/4/05 and 1712/5/05, 1707/5/05 and 1713/5/05	**Primary Care Trust Pharmacist, General Practitioner and Prescribing Adviser v Procter & Gamble and Sanofi-Aventis**	**Actonel mailing**	**Breaches Clauses 7.2 and 10.1**	**No appeal**	**Page 140**
1705/5/05	**Voluntary Admission by Menarini**	**Newspaper article about Migard**	**Breach Clause 20.2**	**No appeal**	**Page 143**
1709/5/05 and 1710/5/05	Pfizer v Lilly and Boehringer Ingelheim	Promotion of Cymbalta	No breach	No appeal	Page 145

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 such medicines made available to the general public.

It covers:

- journal and direct mail advertising
- the activities of representatives, including detail aids and other printed material used by representatives
- the supply of samples
- the provision of inducements to prescribe, supply, administer, recommend or buy medicines by the gift, offer or promise of any benefit or bonus, whether in money or in kind
- the provision of hospitality
- the organisation of promotional meetings
- the sponsorship of scientific and other meetings, including payment of travelling and accommodation expenses
- the provision of information to the general public either directly or indirectly, including by means of the Internet
- all other sales promotion in whatever form, such as participation in exhibitions, the use of audio-cassettes, films, records, tapes, video recordings, electronic media, interactive data systems, the Internet and the like.

Complaints submitted under the Code are considered by the Code of Practice Panel which consists of the three members of the Code of Practice Authority acting with the assistance of independent expert advisers where appropriate. Both complainants and respondents may appeal to the Code of Practice Appeal Board against rulings made by the Panel. The Code of Practice Appeal Board is chaired by an independent legally qualified Chairman, Mr Nicholas Browne QC, and includes independent members from outside the industry.

In each case where a breach of the Code is ruled, the company concerned must give an undertaking that the practice in question has ceased forthwith and that all possible steps have been taken to avoid a similar breach in the future. An undertaking must be accompanied by details of the action taken to implement the ruling. Additional sanctions are imposed in serious cases.

Complaints about the promotion of medicines should be sent to the Director of the Prescription Medicines Code of Practice Authority, 12 Whitehall, London SW1A 2DY (telephone 020 7930 9677 facsimile 020 7930 4554).

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 date on which places remain available is:

Monday, 5 December

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

For further information regarding any of the above, please contact Jean Rollingson for details (020 7930 9677 extn 4).

How to contact the Authority

Our address is:

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

www.pmcpa.org.uk

Telephone: 020 7930 9677
Facsimile: 020 7930 4554

Copies of the Code of Practice for the Pharmaceutical Industry and of this Review can be obtained from Lisa Matthews (020 7930 9677 extn 5).

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

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

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

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